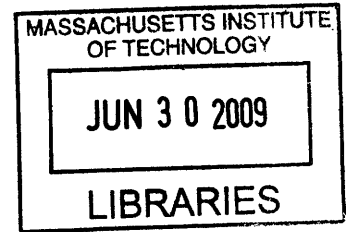


**Development of a Public Health Information Infrastructure
for Postmarket Evidence**

by

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Submitted to the Engineering Systems Division
In Partial Fulfillment of the Requirements for the Degree of
Master of Science in Technology and Policy

at the

Massachusetts Institute of Technology

June 2009

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Abstract

Postmarket data on prescription medical product performance has historically been incomplete, underutilized, and mismanaged to inform safety and comparative clinical effectiveness. Congress has tasked the Food and Drug Administration to build a public health information infrastructure for drug safety. It also has allotted \$1.1 billion dollars in new spending for comparative effectiveness research. A singular, shared, multi-purpose public health information infrastructure can be built to serve both these needs and others. It can be used by multiple public health agencies under a coordinating framework. A new independent public health authority is best positioned to manage that framework and to negotiate the security, legal, proprietary, and privacy barriers that accompany requests to access large amounts of patient data. Such a design protects privacy, avoids duplication, leverages investment, and promotes sustainability in what is truly a "greenfield" opportunity in the United States. Consequently, the policy window to influence the system design is now.

Personal health data is the scarce resource needed to constitute this infrastructure. Citizens have a right and responsibility to re-examine how postmarket data is used to measure safety and comparative clinical effectiveness. A public process to establish new classification schemes that set benefit-risk targets for classes of prescription medical products is needed. Such schemes would differentiate products according to therapeutic need, expected length of treatment, expected patient population, novelty of treatment, and availability of substitutes. These classes would prompt different postmarket requirements according to the needs and values of the affected patient population. Data collection, data analysis, risk management strategies, and reimbursement strategies would logically follow from this classification.

In this paper, inadequate historical postmarket data generation mechanisms and risk management plans are reviewed. Specific attention is given to the failed use of "carrots" and "sticks" to elicit desired behavior. Next, an analysis of stakeholder interests and desired public health outcomes is performed. Policy goals for a public health information infrastructure are outlined along with strategies to achieve those goals.

Thesis Supervisor: Nicholas A. Ashford
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Acknowledgments:

I'd like to thank my thesis supervisor, Prof. Nicholas Ashford, and my husband, Vijay, for all their support and encouragement.

I'd also like to acknowledge my colleagues who have informed my thinking on this matter, specifically Dr. Richard Platt, Dr. Jeffrey Brown, Kimberly Lane, and Beth Syat.

Finally, I'd like to thank my early and continuing support system at MIT including Dr. Gordon Kohse, Dr. Lin-wen Hu, Dr. Gigi Hirsch, and Prof. Deborah Nightingale.

I. Introduction	7
A. Overview of the Problem	8
1. Incomplete and Imperfect Information Generation.....	8
2. Beyond Information Generation: Tackling Ineffective Risk Management.....	18
II. Historical Context	28
A. Overall Differences in the Speed of Innovation.....	28
B. Chloramphenicol: Early Evidence of Postmarket Problems	29
C. Increasing Complexity of Disease States and their Treatments	31
D. The Prescription Drug User Fee Act: A Shift Away from the Postmarket	33
E. Rising Cost of Healthcare, Quality Concerns Drive Evidence-based Medicine.....	36
F. Drug Safety Crises and New Legislation.....	39
III. Inadequate or Failed Solutions to Develop Postmarket Evidence	42
A. The Failed Use of Public "Carrots" to Drive Private Behavior	44
1. Limited Market Incentives for the Conduct of Postmarket Studies	44
2. Failed Market Incentives Targeted to Providers	48
3. Impotent Use of Reimbursement Policies Designed to Develop Evidence	51
B. The Failed Use of Regulatory "Sticks" to Drive Behavior.....	53
1. Mismanaged Spontaneous Reporting Requirements.....	53
2. Impotent Postmarket Study Commitment Enforcement	56
3. Underused Risk Management Programs	58
C. Inconsistent Private Sector Efforts to Develop Postmarket Evidence	61
1. Use of Registries through Private Organizations.	61
2. Litigation	63
IV. Current State Analysis.....	67
A. Key Stakeholders – What are their needs and wants?	67
1. Government Agencies	67
i. FDA	69
ii. AHRQ.....	72
iii. CMS	73
2. Patients	74
3. Providers.....	78
4. Industry.....	81
5. Payors	84
6. Other	85
B. Motivation to Change –Now is the Time.....	86
1. New Internet Technologies Enable Public Involvement.....	88
2. New Technology Investments Signal Opportunities.....	89
3. New Investments in Human Resources are Imminent	90
4. New Legal/Regulatory Schemes Even the Playing Field.....	93
V. Policy Goals for a New Public Health Information Infrastructure	99
A. Broad Needs of a Public Health Information Infrastructure.....	99
1. Safety Concerns.....	99
2. Lack of Comparative Clinical Effectiveness Information.....	100
3. Opportunity Cost associated with Ineffective or Under-effective Therapies.....	101
B. Implementation Goals - How do we get from here to there?	103
1. Legal and Regulatory Implementation Goals.....	103
2. Technology Implementation Goals	108

3.	Scientific Implementation Goals	114
4.	Organizational/Institutional Implementation Goals	117
5.	Social Implementation Goals	120
6.	Private Sector Implementation Goals	120
7.	Summary of Implementation Goals	122
VI.	Policy Strategies	124
A.	Regulatory Strategies	124
B.	Organizational/Institutional Strategies	126
C.	Scientific and Technical Strategies	127
D.	Public Engagement Strategies	128
E.	Cleaning up the Old Legacy	128
VII.	Concluding Comments	130
	Appendix I - List of Acronyms	131
	Bibliography	133

I. Introduction

In recent years, prescription medical products¹ are more pervasive in the daily healthcare routine of Americans than at any other time in history. Between 1998 and 2007, the number of prescriptions dispensed in the United States grew from 2.7 billion to 3.8 billion, representing a 40% increase over a relatively short time period.² Not only is their usage increasing absolutely, but it also appears that Americans are substituting prescription medical products for other healthcare interventions. From 1996 through 2003, prescription drug spending increased from 12% to 20% as a portion of total healthcare expenditures while inpatient hospital stays and ambulatory care proportions decreased.³ Consequently, some health economists argue that prescription-based interventions in certain disease areas like infection, hypertension, and mental health have been among the most cost-effective and necessary inputs to the healthcare system.⁴ However, safe and effective prescription medical product performance varies with a patient's genes, condition, environment, and lifestyle. A product's true clinical value reveals itself over time since significant data are developed on a product's benefits and risks when utilization increases among broader audiences.⁵ These data may change the "known" safety and effectiveness profile of the product relative to substitutes. It is the

¹ Throughout this paper, I use the term prescription medical products to refer both to traditional pharmaceuticals and to therapeutic biological products that are used to improve human health. For more on what qualifies as a therapeutic biological product, see Food and Drug Administration, "Frequently Asked Questions about Therapeutic Biological Products," FDA, <http://www.fda.gov/cder/biologics/qa.htm> (accessed May 2, 2009). Some policy themes will be extensible to medical devices, but medical devices exist under a different regulatory structure that is not addressed in this paper.

² D. K. Wysowski, L. A. Governale and J. Swann, "Trends in Outpatient Prescription Drug Use and Related Costs in the US: 1998-2003," *PharmacoEconomics* 24, no. 3 (2006), 233; IMS National Prescription Audit PLUS, *Data from 2003-2007* (Norwalk, CT: IMS, 2008).

³ S. H. Zuvekas and J. W. Cohen, "Prescription Drugs and the Changing Concentration of Health Care Expenditures," *Health Affairs* 26, no. 1 (Jan-Feb, 2007), 252-253.

⁴ See D. M. Cutler and others, "The Value of Antihypertensive Drugs: A Perspective on Medical Innovation," *Health Affairs* 26, no. 1 (Jan-Feb, 2007), 105-107; and David M. Cutler, *Your Money Or Your Life: Strong Medicine for America's Health Care System* (New York: Oxford University Press, 2004).

⁵ Mara McAdams, "Timing and Characteristics of Safety-Related Actions for New Molecular Entities (1991-2006): A Preliminary Study" Food and Drug Administration, Rockville, MD, 2008). Presentation at the Food and Drug Administration Public Workshop on Maximizing the Public Health Benefit of Adverse Event Collection Throughout a Product's Marketed Life Cycle; K. E. Lasser and others, "Timing of New Black Box Warnings and Withdrawals for Prescription Medications," *Journal of the American Medical Association* 287, no. 17 (May 1, 2002), 2215-2220; U.S. General Accounting Office, *FDA Drug Review: Postapproval Risks, 1976-85*, GAO/PEMD-90-15 (Washington, DC: GPO, 1990), 3.

accurate *collection and conversion of these data into usable knowledge and actionable decision points* that saves social and personal costs to the healthcare system. The Congressional Budget Office (CBO) agreed:

"better information about the costs, risks, and benefits of different treatment options, combined with new incentives reflecting the information, could eventually alter the way in which medicine is practiced and yield lower health care spending without having adverse effects on health."⁶

A. Overview of the Problem

1. Incomplete and Imperfect Information Generation

The current socio-technical infrastructure in place for stakeholders to share, to evaluate, and to comprehend emergent safety and effectiveness data is inadequately structured for decision makers' needs, technologically and logistically outdated, and underfunded. The Institute of Medicine (IOM) noted:

"An irony of the information-rich environment is that information important to clinical decision making is often not available...This is due to too little clinical effectiveness research, too poor dissemination of the evidence that is available, and too few incentives and decision supports for evidence-based care."⁷

As a consequence, stakeholders cannot truly *value* prescription medical products (i.e., the risks, benefits, and costs; the safety and effectiveness relative to substitutes), and thus make irregular and inferior choices regarding their utilization.⁸ Under these conditions, a patient's *informed* consent is less meaningful because it is unclear whether the incomplete and imperfect nature of the available information is well understood.⁹

Public responsibility for generating, managing, and using benefit-risk information on prescription medical products is housed in several public health agencies: regulatory duties in the U.S. Food and Drug Administration (FDA); research-based contributions from the Agency for Healthcare Research and Quality (AHRQ), the Veterans Health

⁶ U.S. Congressional Budget Office, *Research on the Comparative Effectiveness of Medical Treatments: Issues and Options for an Expanded Federal Role* (Washington, DC: Congress of the United States, Congressional Budget Office, 2007), 1-2.

⁷ Institute of Medicine (IOM), *Evidence-Based Medicine and the Changing Nature of Health Care: 2007 IOM Annual Meeting Summary* (Washington, DC: National Academies Press, 2008), 4, <http://www.nap.edu/catalog/12041.html>.

⁸ L. C. Baker, E. S. Fisher and J. E. Wennberg, "Variations in Hospital Resource Use for Medicare and Privately Insured Populations in California," *Health Affairs* 27, no. 2 (Mar-Apr, 2008), w123-34. Also, see the extensive work of the Dartmouth Atlas Project at <http://www.dartmouthatlas.org/agenda.shtml> for research on unwarranted variation in utilization and outcomes of care.

⁹ See discussion in Institute of Medicine (IOM), *Understanding the Benefits and Risks of Pharmaceuticals: Workshop Summary* (Washington, D.C.: National Academies Press, 2007), 39-51, <http://books.nap.edu/openbook.php?isbn=0309107385>.

Administration, and the National Institutes of Health (NIH); and insurance coverage decisions in the Centers for Medicare and Medicaid (CMS), the major public purchaser of healthcare products and services. The accompanying socio-technical infrastructure to collect, interpret, and communicate the information largely depends on whether a product has been approved for use or not. Thus, it is convenient to distinguish these time periods: 1) the time before a product has received approval to be marketed (premarket) and 2) the time that follows (postmarket). This paper will concentrate on the latter.

Briefly, in the premarket, the FDA performs a screening/certification process to answer fundamental questions of safety (i.e., at what dose is a product toxic) and efficacy (i.e., can a product generate the desired therapeutic effect). It reviews a pre-defined information package developed by a product's manufacturer (i.e., sponsor) through controlled clinical experiments or trials. These *explanatory trials* can detect gross and short-term safety signals, but are specifically geared toward proving efficacy by comparing a new treatment to a placebo.¹⁰ Proving efficacy equates to proving a biological mechanism of action. Accordingly, the human subjects selected to participate are recruited to maximize the ability to prove the desired effect. Efficacy – a concept that describes whether an intervention *can be* successful under ideal conditions (i.e., controlled clinical trials) – *is not sufficient* to show effectiveness - a concept that describes whether an intervention *is* successful in real-world clinical conditions (i.e., typical of the postmarket phase of a drug's lifecycle).¹¹ Efficacy is a necessary precondition for effectiveness, but the distribution of possible future effectiveness states is far from a foregone conclusion at the time of marketing.¹² Effectiveness is *formally* studied exclusively in the postmarket either via experimental or randomized studies known interchangeably as pragmatic clinical trials, practical clinical trials, and Phase IV

¹⁰ See comments of Alastair J.J. Wood in S. Okie, "Safety in Numbers--Monitoring Risk in Approved Drugs," *The New England Journal of Medicine* 352, no. 12 (Mar 24, 2005), 1174... "the preapproval system is really designed and powered to detect efficacy' rather than safety..."

¹¹ See B. Haynes, "Can it Work? Does it Work? Is it Worth it? The Testing of Healthcare Interventions is Evolving," *British Medical Journal* 319, no. 7211 (Sep 11, 1999), 652-653... noting that efficacy is a necessary, *but not sufficient*, condition for effectiveness.

¹² B. L. Strom, "Methodologic Challenges to Studying Patient Safety and Comparative Effectiveness," *Medical Care* 45, no. 10 Supl 2 (Oct, 2007), S13-5.

clinical trials¹³; or via observational studies that utilize epidemiologic methods such as case control, cohort, or cross-sectional studies.¹⁴

Numerous reports have noted that the longitudinal effects (i.e., chronic use effects) of new therapeutics may not be apparent during premarket clinical trials, and that the limited and homogenous study populations do not adequately predict performance in the considerably more diverse population at large.¹⁵ Relevant data continues to emerge throughout a product's lifecycle particularly as it is used in new populations, in new dosages, and for new indications. Much of this new use occurs "off-label;" that is, the product is used in a way that has not been tested via premarket clinical trials. On the whole, the premarket knowledge that has been generated is insufficiently generalizable, underdeveloped, and too premature to accurately predict the *evolving benefit-risk performance* of the product, especially for new molecular entities that do not fit into a class of previously marketed products.¹⁶ The IOM has concluded that the multi-phase, premarket product approval system is characterized by an inherent "delayed availability of important safety data until a drug is used in larger and more diverse populations."¹⁷

Yet, public knowledge management on the benefits and risks of prescription medical products *after marketing* is not noticeably better. Available information on adverse drug experiences (i.e., postmarket data) has historically been poorly captured,

¹³ For a descriptions of practical clinical trials, see S. R. Tunis, D. B. Stryer and C. M. Clancy, "Practical Clinical Trials: Increasing the Value of Clinical Research for Decision Making in Clinical and Health Policy," *Journal of the American Medical Association* 290, no. 12 (Sep 24, 2003), 1624-1632; and L. P. Garrison Jr and others, "Using Real-World Data for Coverage and Payment Decisions: The ISPOR Real-World Data Task Force Report," *Value in Health: The Journal of the International Society for Pharmacoeconomics and Outcomes Research* 10, no. 5 (Sep-Oct, 2007), 326-335.

¹⁴ For a brief description of these studies, see Institute of Medicine (IOM), *Knowing what Works in Health Care: A Roadmap for the Nation*, eds. Jill Eden and others (Washington, DC: National Academies Press, 2008), 24.

¹⁵ See Institute of Medicine (IOM), *The Future of Drug Safety: Promoting and Protecting the Health of the Public*, eds. Alina Baci, Kathleen R. Stratton and Sheila P. Burke (Washington, DC: National Academies Press, 2007), 37-39, <http://www.nap.edu/catalog/11750.html>; U.S. Government Accountability Office, *Improvement Needed in FDA's Postmarket Decision-Making and Oversight Process*, GAO-06-402 (Washington, DC: GPO, 2006), 26-28; M. A. Friedman and others, "The Safety of Newly Approved Medicines: Do Recent Market Removals Mean there is a Problem?" *Journal of the American Medical Association* 281, no. 18 (May 12, 1999), 1728-1734.

¹⁶ Institute of Medicine (IOM), *The Future of Drug Safety: Promoting and Protecting the Health of the Public*, 106, *supra* at note 15.

¹⁷ *ibid.*, 38.

catalogued, and assessed.¹⁸ Also, it is unclear whether the data being collected are the *right* data; that is, whether these data generate actionable decision criteria that public health agencies, providers, and patients can use. Without a central public clearinghouse on benefit-risk information, much of the knowledge generated on the performance of products over time is isolated in individual medical practices.

Notably, the dismal performance of the FDA's postmarket efforts has been documented in several reports over a nearly forty-year span.¹⁹ When the FDA does collect data, its focus is overwhelmingly on risk management with regard to safety despite the fact that ineffective or under-effective prescription medical products may also pose risks. Specifically, patients have lost the opportunity to use a more effective product.²⁰ The FDA's emphasis has been driven by politically motivated interpretations of its statutory mandate²¹, and because it seldom is held responsible for knowledge lapses

¹⁸ U.S. General Accounting Office, *Adverse Events: The Magnitude of Health Risk is Uncertain because of Limited Incidence Data*, GAO/HEHS-00-21 (Washington, DC: GPO, 2000), 10, citing Steven A. Goldman and others, *The Clinical Impact of Adverse Event Reporting* (Rockville, MD: Food and Drug Administration, Center for Drug Evaluation and Research, 1996).

¹⁹ See generally Drug Research Board, National Research Council, *Report of the International Conference on Adverse Reaction Reporting Systems* (Washington, DC: National Academy of Sciences, 1971); U.S. General Accounting Office, *Assessment of the Food and Drug Administration's Handling of Reports on Adverse Reactions from the Use of Drugs* (Washington, DC: GPO, 1974); Joint Commission on Prescription Drug Use, *The Final Report of the Joint Commission on Prescription Drug Use* (Rockville, MD, 1980); U.S. General Accounting Office, *FDA can further Improve its Adverse Drug Reaction Reporting System: Report to the Secretary of Health and Human Services*, HRD-82-37 (Washington, DC: GPO, 1982); U.S. Office of Technology Assessment, *Postmarketing Surveillance of Prescription Drugs*, OTA-H-189 (Washington, DC: Congress of the United States, Office of Technology Assessment, 1982); U.S. General Accounting Office, *FDA Drug Review: Postapproval Risks, 1976-85*, *supra* at note 5; U.S. Government Accountability Office, *Improvement Needed in FDA's Postmarket Decision-Making and Oversight Process*, *supra* at note 15.

²⁰ See, for example, C. A. Jackevicius and others, "Use of Ezetimibe in the United States and Canada," *The New England Journal of Medicine* 358, no. 17 (Apr 24, 2008), 1819-1828; and H. M. Krumholz and T. H. Lee, "Redefining Quality--Implications of Recent Clinical Trials," *The New England Journal of Medicine* 358, no. 24 (Jun 12, 2008), 2537-2539. They describe increases in prescriptions for a new medication, which was substituted for a generic product with proven benefits in long-term morbidity and mortality. There was considerable controversy when the new medication subsequently failed to demonstrate comparably beneficial outcomes in clinical trials. See U.S. Senate Committee on Finance and C. Grassley, "Memorandum to Reporters and Editors on the Vytorin Study," U.S. Senate Committee on Finance, <http://finance.senate.gov/press/Gpress/2008/prg033108.pdf> (accessed January 19, 2009); and Alex Berenson, "For Widely Used Drug, Question of Usefulness is Still Lingering," *The New York Times*, sec. A, September 2, 2008.

²¹ P. Lurie and L. D. Sasich, "Safety of FDA-Approved Drugs," *Journal of the American Medical Association* 282, no. 24 (Dec 22-29, 1999), 2297-2298... In response to a Letter to the Editor, the FDA states that it "can only judge a product's safety and efficacy not its uniqueness of comparative efficacy or its social value." However, this statement is contrary to the FDA's practice of designating certain new drugs for a faster review because of their therapeutic significance. See Food and Drug Administration, "Review Classification Policy: Priority (P) and Standard (S)," FDA, <http://www.fda.gov/cder/mapp/6020.3R.pdf>

in effectiveness. Recent notable postmarket failures in safety - selective serotonin reuptake inhibitors (SSRIs)²² and Vioxx™ (rofecoxib)²³ – renewed national interest in the FDA's performance in this area, and culminated in explicit new funding and authority in the Food and Drug Administration Amendments Act (FDAAA) of 2007.²⁴ The FDA's launch of the Safety First Initiative²⁵ and the Sentinel Initiative²⁶ have clearly carved out safety as the FDA's responsibility, leaving management of data on the clinical and comparative effectiveness of prescription medical products to other agencies.

In that regard, until perhaps recently, the Agency for Healthcare Research and Quality (AHRQ) has had a limited capacity and budget to generate postmarket evidence by commissioning research studies on outcomes to compare treatments (e.g., studying the best first course treatment for diabetes). This type of information is important in crowded therapeutic classes when rigorous comparisons among like treatments do not exist, and direct-to-consumer advertising (DTCA) and physician promotion activities may drive healthcare decisions in the absence of better information.²⁷ As the former head of the AHRQ – then the Agency for Health Care Policy and Research (AHCPR) - explained:

"The purposes of the FDA's approval process and AHCPR's technology assessments are quite different and in no way redundant. FDA approval to market a drug or medical device is based on an analysis of the manufacturer's claims for the product. The FDA does not compare the effectiveness of a drug or device with alternative products. Also, the FDA generally does not review a product after it had been approved for marketing in

(accessed March 20, 2009). Classification schemes that privilege certain new drugs date back to at least 1980. See U.S. General Accounting Office, *FDA Drug Approval: A Lengthy Process that Delays the Availability of Important New Drugs*, HRD-80-64 (Washington, DC: GPO, 1980), 4-6.

²² See U.S. House Committee on Energy and Commerce, *FDA's Role in Protecting the Public Health: Examining FDA's Review of Safety and Efficacy Concerns in Anti-Depressant Use by Children*, 108th Cong., 2d sess., 2005.

²³ See U.S. Senate Committee on Finance, *FDA, Merck, and Vioxx: Putting Patient Safety First?* 108th Cong., 2d sess., 2005.

²⁴ Title IX: Enhanced Authorities Regarding Postmarket Safety of Drugs in *Food and Drug Administration Amendments Act of 2007*, Public Law 110-85, *Statutes at Large* 121 (September 27, 2007), 823-978, codified in various sections of 21 U.S.C. § 331, 334, 352, 353, 355, 360, 381.

²⁵ U.S. Senate Committee on Finance and C. Grassley, "Grassley Says Changes to Improve FDA Post-Market Review Remain Elusive," U.S. Senate Committee on Finance, <http://finance.senate.gov/press/Gpress/2008/prg031308b.pdf> (accessed January 19, 2009).

²⁶ U.S. Department of Health and Human Services, Food and Drug Administration, *The Sentinel Initiative: A National Strategy for Monitoring Medical Product Safety* (Rockville, MD: FDA, May 2008), <http://www.fda.gov/oc/initiatives/advance/reports/report0508.html> (accessed July 1, 2008).

²⁷ U. E. Reinhardt, "An Information Infrastructure for the Pharmaceutical Market," *Health Affairs* 23, no. 1 (Jan-Feb, 2004), 107-112.

order to gauge its continuing clinical effectiveness. Such postmarketing review of products is a principal justification for technology assessments undertaken by AHCPR."²⁸

The AHCPR first began health technology assessment efforts specifically targeted at pharmaceuticals in 1992.²⁹ Historically, these studies have been systematic reviews and synthesis of existing evidence, or retrospective analyses of claims and clinical data.³⁰ Initial evaluations of the program by the Office of Technology Assessment (OTA)³¹ and others³² criticized the methodology as costly, potentially duplicative of other private sector efforts, and unreliable because of potential biases in nonrandomized data. Testimony from the General Accounting Office (GAO) indicated that clinicians were unlikely to use clinical practice guidelines that had been generated from the synthesized evidence because the guidelines were too lengthy, complex, and broad in scope.³³ These unfavorable assessments, coupled with a troubled political history, resulted in an overhaul of the AHCPR's name, budget, and duties.³⁴

The agency's internal evidence synthesis programs were eliminated³⁵ in favor of federally funded, extramural Centers for Education and Research on Therapeutics (CERTs), which were tasked with "the conduct of research on the comparative

²⁸ J. Jarrett Clinton, "Agency for Health Care Policy and Research: Overview of Purpose and Programs," *Food and Drug Law Journal* 49 (1994), 458.

²⁹ Robert T. Angarola and Brian L. Pendleton, "The Agency for Health Care Policy and Research and the Pharmaceutical Industry," *Food and Drug Law Journal* 48 (1993), 513-521.

³⁰ G. R. Wilensky, "Developing a Center for Comparative Effectiveness Information," *Health Affairs* 25, no. 6 (Nov-Dec, 2006), w572-85. For a description of the systematic review process, see also U.S. Office of Technology Assessment, *Identifying Health Technologies that Work: Searching for Evidence*, OTA-H-608 (Washington, DC: Congress of the United States, Office of Technology Assessment, 1994), Appendix C.

³¹ *ibid.*, 3-17..."Administrative databases generally have not proved useful in answering questions about the comparative effectiveness of alternative medical treatments."

³² See discussion in C. Anderson, "Measuring what Works in Health Care," *Science* 263, no. 5150 (Feb 25, 1994), 1080-1082.

³³ U.S. General Accounting Office and Sarah F. Jaggar, *Practice Guidelines: Overview of Agency for Health Care Policy and Research Efforts*, GAO/T-HEHS-95-221 (Washington, DC: GPO, 1995), 5-8.

³⁴ J. M. Eisenberg, "The Agency for Healthcare Research and Quality: New Challenges, New Opportunities," *Health Services Research* 35, no. 1 Pt 1 (Apr, 2000), xi-xvi; See also U.S. Congressional Budget Office, *Research on the Comparative Effectiveness of Medical Treatments: Issues and Options for an Expanded Federal Role*, table 1 on 10, *supra* at note 6, for a chart of the AHRQ's annual appropriations history.

³⁵ B. H. Gray, M. K. Gusmano and S. R. Collins, "AHCPR and the Changing Politics of Health Services Research," *Health Affairs* Suppl Web Exclusives (Jan-Jun, 2003), w3-303, quoting the Director of the AHRQ, "The strategy of AHRQ partnering with professional groups and others to use evidence reports that we have sponsored to write guidelines is the way to get them written well, and it is a model more likely to succeed than the old AHCPR model."

effectiveness, cost-effectiveness and safety of drugs, biological products, and devices."³⁶ In truth, the CERTs program has been minimally funded and has not yielded a sizable impact on providers and their patients.³⁷ The AHRQ has another mandate for comparative effectiveness research to address the priorities of the CMS and the State Children's Health Insurance Program (SCHIP).³⁸ These comparative effectiveness activities, conducted through the AHRQ's Effective Health Care Program, have encompassed between 5-10% of the agency's budget, but have been shared among prescription medical products, medical/surgical procedures, and diagnostic tests.³⁹ Overall, the AHRQ has the statutory mandates to perform research, but has been routinely underfunded to do so.

As part of the 2009 federal effort to stimulate the economy, Congress - via the American Recovery and Reinvestment Act (ARRA) of 2009⁴⁰ - appropriated an additional \$1.1 billion for comparative effectiveness research, a windfall when compared to historical efforts. Of that amount, \$300 million is designated to supplement the

³⁶ Sec. 912(b): Centers for Research and Education on Therapeutics in *Healthcare Research and Quality Act of 1999*, Public Law 106-129, *Statutes at Large* 113 (December 6, 1999), 1653-1677, codified at 42 U.S.C. § 299b-1, which established the CERTs under the leadership of the AHRQ in consultation with the Commissioner of the FDA. See also Sec. 409 in *Food and Drug Administration Modernization Act of 1997*, Public Law 105-115, *Statutes at Large* 111 (November 21, 1997), 2296-2380, which is the earlier legislation that first established the CERTs as a pilot research project.

³⁷ The budget request for the CERTs for FY09 was \$10.9 million, up from \$3 million since the program's inception. For more, see Agency for Healthcare Research and Quality, "Budget Estimates for Appropriations Committees, Fiscal Year 2009," AHRQ, <http://www.ahrq.gov/about/cj2009/cjweb09a.htm> (accessed March 31, 2009). See also Tunis, Stryer and Clancy, *Practical Clinical Trials: Increasing the Value of Clinical Research for Decision Making in Clinical and Health Policy*, 1628, *supra* at note 13... "the annual funding [of the CERTs] is adequate to identify *but not support* important PCTs [practical clinical trials] related to pharmaceutical therapies." (emphasis added)

³⁸ Sec. 1013: Research on Outcomes of Health Care Items and Services in *Medicare Prescription Drug, Improvement, and Modernization Act of 2003*, Public Law 108-173, *Statutes at Large* 117 (December 8, 2003), 2066-2480, codified at 42 U.S.C. § 299b-7... "To improve the quality, effectiveness, and efficiency of health care delivered pursuant to the programs established under titles XVIII, XIX, and XXI of the Social Security Act, the Secretary acting through the Director of the Agency for Healthcare Research and Quality (in this section referred to as the 'Director'), shall conduct and support research to meet the priorities and requests for scientific evidence and information identified by such programs with respect to--
(i) the outcomes, comparative clinical effectiveness, and appropriateness of health care items and services (including prescription drugs);"

³⁹ In FY09, the AHRQ's total budget request was \$325M, and the Effective Health Care Program request was \$30M, a doubling of the previous \$15M allocated per year from FY04-FY08. For more, see Agency for Healthcare Research and Quality, *Budget Estimates for Appropriations Committees, Fiscal Year 2009*, *supra* at note 37.

⁴⁰ Title VIII: Departments of Labor, Health and Human Services, and Education, and Related Agencies in *American Recovery and Reinvestment Act of 2009*, Public Law 111-5, *Statutes at Large* 123 (February 17, 2009), 115-522.

Effective Health Care program, an amount that nearly matches the AHRQ's entire annual operating budget in recent years.⁴¹ The recent legislation also created the Federal Coordinating Council for Comparative Effectiveness Research, which will guide federal priorities for new research and have a significant impact on the future of public health evidence generation.⁴²

The NIH also was allotted \$400 million for comparative effectiveness research via the ARRA.⁴³ These monies represent a significant increase in the NIH's comparative effectiveness budget over previous years, but are a minor component of the overall budget, which favors basic research that primes the engine of new drug development.⁴⁴ The NIH typically becomes involved in comparative effectiveness research when smaller studies are inconclusive or lack rigor such that new evidence must be generated through head-to-head, randomized controlled trials. The NIH has funded several large-scale comparative effectiveness trials: the Women's Health Initiative (WHI) trial at \$725M; the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) at \$125M; the Clinical Anti-Psychotic Trials of Intervention Effectiveness (CATIE) at \$60M; and currently, the Comparison of Age-related Macular Degeneration Treatments Trials (CATT).⁴⁵ Similarly, the Veterans Health Administration, via its Cooperative Studies Program, has studied various pharmacotherapies to treat benign prostatic hyperplasia.⁴⁶ These clinical trials are multi-year efforts to collect new data. They are infrequent because of the time and expense involved in their execution. Consequent with its new appropriations, the NIH is funding both clinical trials and

⁴¹ See Agency for Healthcare Research and Quality, *Budget Estimates for Appropriations Committees, Fiscal Year 2009*, *supra* at note 37.

⁴² Sec. 804: Federal Coordinating Council for Comparative Effectiveness Research in *American Recovery and Reinvestment Act of 2009, Public Law 111-5*.

⁴³ Title VIII: Departments of Labor, Health and Human Services, and Education, and Related Agencies in *American Recovery and Reinvestment Act of 2009, Public Law 111-5*.

⁴⁴ The FY08 budget for the NIH was \$29.3B. See National Institutes of Health Office of the Budget, "Budget Information," NIH, <http://officeofbudget.od.nih.gov/ui/HomePage.htm> (accessed March 31, 2009).

⁴⁵ See Institute of Medicine (IOM), *The Future of Drug Safety: Promoting and Protecting the Health of the Public*, 115, *supra* at note 15, for a description of all but the CATT.

⁴⁶ H. Lepor and others, "The Efficacy of Terazosin, Finasteride, Or both in Benign Prostatic Hyperplasia. Veterans Affairs Cooperative Studies Benign Prostatic Hyperplasia Study Group," *The New England Journal of Medicine* 335, no. 8 (Aug 22, 1996), 533-539.

epidemiologic analyses, but also has directed focus to the public health information infrastructure that will be necessary for large-scale data sharing.⁴⁷

Notably, neither the FDA⁴⁸, the Effective Health Care Program of the AHRQ⁴⁹, nor the CMS⁵⁰ is explicitly authorized to consider the cost-effectiveness of prescription medical products in decision-making or agenda-setting, which is a sharp contrast from agencies such as the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom. However, the high out-of-pocket costs of prescription medical products may cause patients to forego their use, creating potential complications and greater medical expenses later. Studies have shown that higher costs reduce patient compliance and contribute to increased mortality and morbidity.⁵¹

All told, healthcare providers and patients lack a continuous and accurate stream of knowledge on how medical products perform in real-world conditions, i.e. on populations with co-morbidities, chronic illnesses, and multiple prescriptions/polypharmacy. There is no unifying, centrally-coordinated effort that develops and houses knowledge on safety with clinical and cost effectiveness despite the fact that these concepts are clearly complimentary and interdependent. Over the years, many academics and policymakers have called for an independent public health information infrastructure to deal with emergent information on prescription medical

⁴⁷ For a list of the research projects that the NIH intends to support with its new funding, see U.S. Department of Health and Human Services and Office of Extramural Research at National Institutes of Health, "NIH Challenge Grants in Health and Science Research (RC1)," NIH, http://grants.nih.gov/grants/funding/challenge_award/ (accessed March 31, 2009). See particularly, 05-AG-101 - Data Infrastructure for Post-Marketing Comparative Effectiveness Studies.

⁴⁸ Institute of Medicine (IOM), *The Future of Drug Safety: Promoting and Protecting the Health of the Public*, 39, 126, *supra* at note 15; Lurie and Sasich, *Safety of FDA-Approved Drugs*, 2297-2298, *supra* at note 21.

⁴⁹ Wilensky, *Developing a Center for Comparative Effectiveness Information*, w575, *supra* at note 30, noting "There is no provision for the use of cost-effectiveness information in [the Medicare Modernization Act] which presumably reflects continued sensitivity to the use of that type of analysis in Medicare's decision making."

⁵⁰ *ibid.*, w584... "To date, the United States has been unwilling to include statutory language that would allow cost-effectiveness information to be used in making coverage decisions even in large public programs such as Medicare."

⁵¹ See J. Hsu and others, "Unintended Consequences of Caps on Medicare Drug Benefits," *The New England Journal of Medicine* 354, no. 22 (Jun 1, 2006), 2349-2359; D. W. Roblin and others, "Effect of Increased Cost-Sharing on Oral Hypoglycemic use in Five Managed Care Organizations: How Much is Too Much?" *Medical Care* 43, no. 10 (Oct, 2005), 951-959; D. P. Goldman and others, "Pharmacy Benefits and the Use of Drugs by the Chronically Ill," *Journal of the American Medical Association* 291, no. 19 (May 19, 2004), 2344-2350; A. D. Federman and others, "Supplemental Insurance and Use of Effective Cardiovascular Drugs among Elderly Medicare Beneficiaries with Coronary Heart Disease," *Journal of the American Medical Association* 286, no. 14 (Oct 10, 2001), 1732-1739.

products. Unfortunately, most have advocated models that appear to preserve the present-day information silos by isolating questions of drug safety in the postmarket⁵² from comparative clinical effectiveness or outcomes research.⁵³ A minority has combined the two ideas, suggesting a clearinghouse-type Center for Drug Information that would meet multiple needs.⁵⁴

As noted above, both the FDA⁵⁵, and the Department of Health and Human Services (DHHS) and its subordinate agencies⁵⁶, have received new monies and new responsibilities to build such an infrastructure(s) to suit their needs. The requirements for an infrastructure(s) are similar to modern networks used in financial systems or air traffic control; that is hardware and software components must be interoperable and subscribe to

⁵² For a non-exhaustive list, see T. J. Moore, B. M. Psaty and C. D. Furberg, "Time to Act on Drug Safety," *Journal of the American Medical Association* 279, no. 19 (May 20, 1998), 1571-1573; A. J. Wood, C. M. Stein and R. Woosley, "Making Medicines Safer--the Need for an Independent Drug Safety Board," *The New England Journal of Medicine* 339, no. 25 (Dec 17, 1998), 1851-1854; Jerry Avorn, *Powerful Medicines: The Benefits, Risks, and Costs of Prescription Drugs*, 1st ed. (New York: Knopf, 2004); P. B. Fontanarosa, D. Rennie and C. D. DeAngelis, "Postmarketing Surveillance--Lack of Vigilance, Lack of Trust," *Journal of the American Medical Association* 292, no. 21 (Dec 1, 2004), 2647-2650; M. M. Reidenberg, "Improving how we Evaluate the Toxicity of Approved Drugs," *Clinical Pharmacology and Therapeutics* 80, no. 1 (Jul, 2006), 1-6.

⁵³ See Reinhardt, *An Information Infrastructure for the Pharmaceutical Market*, 107-112, *supra* at note 27; Wilensky, *Developing a Center for Comparative Effectiveness Information*, w572-85, *supra* at note 30; Billy Beane, Newt Gingrich and John Kerry, "How to Take American Health Care from Worst to First," *The New York Times*, Editorial, October 24, 2008.

⁵⁴ See W. A. Ray and C. M. Stein, "Reform of Drug Regulation--Beyond an Independent Drug-Safety Board," *The New England Journal of Medicine* 354, no. 2 (Jan 12, 2006), 194-201; B. L. Strom, "How the US Drug Safety System Should be Changed," *Journal of the American Medical Association* 295, no. 17 (May 3, 2006), 2072-2075; Joint Commission on Prescription Drug Use, *The Final Report of the Joint Commission on Prescription Drug Use*, *supra* at note 19; Drug Research Board, National Research Council, *Report of the International Conference on Adverse Reaction Reporting Systems*, *supra* at note 19.

⁵⁵ Sec. 905: Active Postmarket Risk Identification and Analysis in *Food and Drug Administration Amendments Act of 2007, Public Law 110-85*, codified at 21 U.S.C. § 355(k)(3)(B)(ii). ... "The Secretary shall... (ii) develop validated methods for the establishment of a postmarket risk identification and analysis system to link and analyze safety data from multiple sources, with the goals of including, in aggregate— (I) at least 25,000,000 patients by July 1, 2010; and (II) at least 100,000,000 patients by July 1, 2012;" See commentary in Barbara J. Evans, "Congress' New Infrastructural Model of Medical Privacy," *Notre Dame Law Review* 84 (January 2009), 585-654.

⁵⁶ Title VIII: Departments of Labor, Health and Human Services, and Education, and Related Agencies in *American Recovery and Reinvestment Act of 2009, Public Law 111-5*... "That the funding appropriated in this paragraph shall be used to accelerate the development and dissemination of research assessing the comparative effectiveness of health care treatments and strategies, through efforts that... encourage the development and use of clinical registries, clinical data networks, and other forms of electronic health data that can be used to generate or obtain outcomes data."

common communication protocols and standards. The IOM extends this metaphor by calling for "the establishment of healthcare data as a public good."⁵⁷

This paper argues that a singular public authority is best equipped to navigate the transaction costs associated with the security, legal, proprietary, and privacy barriers that accompany requests to access large amounts of patient data.⁵⁸ Also, the similarities in the required data favor a single, multi-purpose effort that is shared across the agencies. Such a common infrastructure has the potential to save time, effort, and cost by avoiding duplicative or redundant efforts. Accessing these data to generate collective knowledge on the safe and effective real-world use of prescription medical products requires a paradigm change: one that privileges a unified and cohesive systems-level approach above the fragmented efforts of numerous public and private stakeholders.

2. Beyond Information Generation: Tackling Ineffective Risk Management

As technologies advance, societies commonly face the challenges of coping with uncertain scientific and technical information when formulating public policy. Most of the time, first courses of action include developing methods to generate and evaluate the unknown or uncertain information. However, when that uncertainty pertains to potential health and safety risks, there is a potential harm in delaying decision-making while waiting for better information to be developed. In the parlance of uncertainty and risk management, there is a *value-of-information* that is often quantitatively assessed using decision analysis frameworks.⁵⁹ In order to justify the time spent acquiring new information and delaying action, the new information must be expected to meaningfully influence the decision-maker's preferred actions.⁶⁰ In the postmarket, the period of significant uncertainty follows a major decision point (market approval), and so it may

⁵⁷ Institute of Medicine (IOM), *Learning Healthcare System Concepts v2008: Annual Report* (Washington, DC: National Academies Press, 2008), v, <http://www.iom.edu/File.aspx?ID=57381>.

⁵⁸ Evans, *Congress' New Infrastructural Model of Medical Privacy*, 595-596, *supra* at note 55... "It is infeasible for a private, commercial database operator to obtain all the individual authorizations (or waiver of authorizations) that would be needed to obtain identifiable information for 25 to 100 million people. Moreover, even if private entities could assemble such a database, it would need ongoing regulation to protect the privacy of persons whose data are included."

⁵⁹ National Research Council, *Science and Decisions: Advancing Risk Assessment* (Washington, DC: National Academies Press, 2008), 80-85, http://www.nap.edu/catalog.php?record_id=12209.

⁶⁰ *ibid.*, 82... "In a VOI analysis, an information source is valued solely on the basis of the probability and magnitude of its potential impacts on a specific decision at a specific time with a specific state of prior knowledge."

seem counterintuitive to suggest that data still need to be collected, that the job is not complete. However, it is not the scientific uncertainty in describing a biological mechanism of action that demands collection and management of postmarket data. Rather, it is an entirely new phase of uncertainty in a product's lifecycle caused by emergent interactions in more complex patient populations. These new users are administered innovative products by providers with a wide range of skill and knowledge levels. A former Commissioner of the FDA observed:

"At the time of approval, the FDA's knowledge-base may be close to perfect, but it is also highly limited because, at that point, the drug has been tested on a relatively small population of patients. Once the drug enters the marketplace, risks that are relatively rare, that manifest themselves only after an extended period of time, or that affect vulnerable subpopulations, begin to emerge."⁶¹

During this interim time when new evidence is being developed on prescription medical products, the government has a responsibility to advance utilization in a socially beneficial way (i.e., communicating the limits of knowledge to providers and patients, and gathering new knowledge that is *materially important* to decision-making and risk management) while actively controlling for the adverse effects of the new technologies (i.e., adequately guarding against significant and unanticipated side effects).

There are active disagreements on the role of the government in the restriction of private risk-taking behaviors, and the appropriate role of the precautionary principle.⁶² The precautionary principle encourages special consideration of protective action in situations of scientific uncertainty in which substantial or irreversible harms are possible.⁶³ This is especially embodied in the "first, do no harm" medicine paradigm. These views are often emotionally charged and highly circumstantial. "First, do no harm" (i.e., precaution or watchful waiting) may be seen as *more harmful* under certain conditions, as illustrated by a recent court case arguing that terminally ill patients have a

⁶¹ David A. Kessler and David C. Vladeck, "A Critical Examination of the FDA's Efforts to Preempt Failure-to-Warn Claims," *Georgetown Law Journal* 96 (January 2008), 466.

⁶² See discussion in Institute of Medicine (IOM), *Understanding the Benefits and Risks of Pharmaceuticals: Workshop Summary*, 49-51, *supra* at note 9, entitled "Paternalism v. Libertarianism;" and Richard A. Epstein, "Regulatory Paternalism in the Market for Drugs: Lessons from Vioxx and Celebrex," *Yale Journal of Health Policy Law and Ethics* 5 (Summer 2005), 741-770.

⁶³ Nicholas Ashford, "The Legacy of the Precautionary Principle in US Law: The Rise of Cost-Benefit Analysis and Risk Assessment as Undermining Factors in Health, Safety and Environmental Protection" In *Implementing the Precautionary Principle: Approaches from Nordic Countries, EU, and USA*, ed. N. Sadeleer (London: Earthscan Publ. Ltd, 2006), 354.

constitutional right to access experimental (or premarket) drugs.⁶⁴ Additionally, the distribution of risks and benefits in "private" risk-taking behaviors are not necessarily borne by the individual alone because of the nature of risk-pooling in health insurance and the collective costs of the U.S. healthcare system. Consequently, there is a significant collective stake in what seem to be strictly individual health behaviors.

History has shown that the dangerous nature of medical products and severity of information asymmetry favors government policy intervention beyond simply policing the use of information and providing accurate data to stakeholders. In fact, expanded FDA authority first resulted from fatalities that occurred immediately after using *properly labeled* medical products.⁶⁵ Much to the chagrin of neo-classical economists and libertarians⁶⁶, later expansions of the FDA's authority⁶⁷ increased its ability to act as a scientific gatekeeper for trade in medical products by establishing standards of safety and efficacy that products must meet *before* they are available to the public.

This gatekeeping function calls for continuous judgment of the needs of the individual and the needs of the collective, and the predicted behavior of both. The FDA makes decisions on medical products based on their perceived effect on the *population as a whole*, which may restrict the treatment options of individual patients and physicians that would be willing to assume more risk. That is, the FDA tends to be utilitarian: products are allowed on the market when it is believed that more damage would be inflicted on the population at large if access to the product were withheld. The FDA must balance the potential error of allowing a high-risk and possibly unsafe product to gain market entry or remain on the market because it provides some uncertain degree of value

⁶⁴ *Abigail Alliance for Better Access to Developmental Drugs v. Von Eschenbach*, No. 04-5350, 378 (U.S. App. D.C. 2007); and commentary in Rebecca S. Eisenberg, "The Role of the FDA in Innovation Policy," *Michigan Telecommunications and Technology Law Review* 13 (Spring 2007), 367-368... "Justifications for the FDA's roles that focus on protecting patients from harm invite the objection that patients may be harmed by disease as well as by drugs... The [appellate] court held that the FDA's policy of denying such access [to experimental drugs] impinged upon substantive due process rights to privacy, liberty and life."

⁶⁵ See Philip J. Hilts, *Protecting America's Health: The FDA, Business, and One Hundred Years of Regulation* (New York: Alfred A. Knopf, 2003), 89-91, describing the elixir Sulfanilamide tragedy.

⁶⁶ See objections in Sam Peltzman, *Regulation of Pharmaceutical Innovation: The 1962 Amendments* (Washington: American Enterprise Institute for Public Policy Research, 1974); and William M. Wardell and Louis Lasagna, *Regulation and Drug Development* (Washington: American Enterprise Institute for Public Policy Research, 1975). For more recent arguments, see D. Klein, "Policy Medicine Versus Policy Quackery: Economists Against the FDA," *Knowledge, Technology, and Policy* 13, no. 1 (2000), 92-101.

⁶⁷ *Drug Amendments of 1962*, Public Law 87-781, *Statutes at Large* 76 (October 10, 1962), 780-796. These are also known as the Kefauver-Harris Amendments.

(deemed a "Type I" error) against the error of removing or severely restricting the use of a product based on limited initial information when the avoided use produces harm (deemed a "Type II" error). This decision-making algorithm produces different outcomes for different patients depending on their personal circumstances, and yet the FDA must choose one fine-line distinction based on the collective. In other words, it must perform a value-of-information analysis on behalf of society. Such an analysis is meaningless if the data collected do not provide logical and actionable decision points for interested stakeholders.

Generally, providing balanced information to inform choices *is not enough*. Results from the ALLHAT trial, which showed that inexpensive diuretics were the best first course treatment for hypertension, have failed to make the anticipated impact in medical communities.⁶⁸ Two studies conducted by the FDA and several healthcare maintenance organizations found that the addition of a "Dear Healthcare Professional Letter" and boxed warnings on Propulsid™ (cisapride)⁶⁹ and Rezulin™ (troglitazone)⁷⁰ did not appreciably change contraindicated uses (i.e., use of a product even though a patient's health conditions should preclude such use). Both drugs were voluntarily removed from the market by their sponsors. Phenformin, an anti-diabetes drug, was removed *twenty years earlier for the same reason*: the inability to mitigate against unapproved and dangerous uses.⁷¹ Others have noted the potential benefits that Vioxx™ (rofecoxib) may have provided to those with severe arthritis who were also at risk of gastrointestinal bleeding⁷², and cited the over-prescription of the drug to inappropriate patients as the major error in its use.⁷³ These examples all point to systemic, historically

⁶⁸ Andrew Pollack, "A Big Blood Pressure Study, and its Minimal Impact on Drug Use," *The New York Times*, sec. B, November 28, 2008.

⁶⁹ W. Smalley and others, "Contraindicated Use of Cisapride: Impact of Food and Drug Administration Regulatory Action," *Journal of the American Medical Association* 284, no. 23 (Dec 20, 2000), 3036-3039.

⁷⁰ D. J. Graham and others, "Liver Enzyme Monitoring in Patients Treated with Troglitazone," *Journal of the American Medical Association* 286, no. 7 (Aug 15, 2001), 831-833.

⁷¹ David A. Kessler, "Regulating the Prescribing of Human Drugs for Nonapproved Uses Under the Food, Drug, and Cosmetic Act," *Harvard Journal of Legislation* 15 (1977), 733-737.

⁷² Institute of Medicine (IOM), *Understanding the Benefits and Risks of Pharmaceuticals: Workshop Summary*, 23, *supra* at note 9; and S. Okie, "Raising the Safety Bar--the FDA's Coxib Meeting," *The New England Journal of Medicine* 352, no. 13 (Mar 31, 2005), 1283.

⁷³ Institute of Medicine (IOM), *Understanding the Benefits and Risks of Pharmaceuticals: Workshop Summary*, 49, *supra* at note 9.

unresolved issues in which individuals who may have benefitted from a product were unable to use it because of the aggregate behaviors of all users.

The CMS has similarly been described as a gatekeeper because its national coverage decisions (NCDs), premised on a finding that a treatment meets the legal standard of "reasonable and necessary" care⁷⁴, can impact the access to prescription medical products. CMS's policies generally influence the coverage decisions of other public and private payors such that a non-coverage determination severely limits the utilization of that technology.⁷⁵ NCDs override any local coverage decisions and require a showing of clinical evidence of effectiveness.⁷⁶ Prior to the early 1980s, the threshold for that showing was relatively low; healthcare services were generally "reasonable and necessary" if a provider deemed them so.⁷⁷ The situation irreversibly shifted when the costs of the Medicare program began to climb both because of the availability of new technologies and services, and the essentially unlimited coverage of those services.⁷⁸ Agencies like the OTA, the AHRQ, and its predecessors arose from a Congressional desire to generate health outcomes evidence to support coverage decisions; these aims were vigorously contested for their implicit cost control considerations.⁷⁹

Since then, the CMS's coverage policies have been mired in controversy over the ability to consider cost-effectiveness as a criterion when making a "reasonable and necessary" determination. In fact, there have been multiple failed attempts to promulgate

⁷⁴ Sec. 1862(a)(1)(A): Exclusions from Coverage in *Social Security Amendments of 1965*, Public Law 89-97, *Statutes at Large* 79 (July 30, 1965), 286-423, codified at 42 U.S.C. § 1395y(a).

⁷⁵ Sandra J. Carnahan, "Medicare's Coverage with Study Participation Policy: Clinical Trials Or Tribulations?" *Yale Journal of Health Policy, Law and Ethics* 7 (Summer 2007), 235.

⁷⁶ *ibid.*, 236-239.

⁷⁷ S. R. Tunis, "Why Medicare has Not Established Criteria for Coverage Decisions," *The New England Journal of Medicine* 350, no. 21 (May 20, 2004), 2196.

⁷⁸ Eleanor D. Kinney, "Medicare Coverage Decision-Making and Appeal Procedures: Can Process Meet the Challenge of New Medical Technology?" *Washington & Lee Law Review* 60 (Fall 2003), 1467; and J. M. Eisenberg and D. Zarin, "Health Technology Assessment in the United States: Past, Present, and Future," *International Journal of Technology Assessment in Health Care* 18, no. 2 (Spring 2002), 193.

⁷⁹ See Gray, Gusmano and Collins, *AHCPR and the Changing Politics of Health Services Research*, w3-304, *supra* at note 35 ... "The goal of achieving cost containment was vested heavily in the [AHCPR's] mandate to develop and disseminate practice guidelines." See also U.S. Office of Technology Assessment, *Identifying Health Technologies that Work: Searching for Evidence*, 132-135, *supra* at note 31; Carnahan, *Medicare's Coverage with Study Participation Policy: Clinical Trials Or Tribulations?*, 229-272, *supra* at note 75; Kinney, *Medicare Coverage Decision-Making and Appeal Procedures: Can Process Meet the Challenge of New Medical Technology?*, footnote 47, *supra* at note 78; and J. E. Wennberg, "Outcomes Research, Cost Containment, and the Fear of Health Care Rationing," *The New England Journal of Medicine* 323, no. 17 (Oct 25, 1990), 1202-1204.

a national standard for criteria and interpretation of "reasonable and necessary."⁸⁰ However, few are willing to argue that the CMS should be reimbursing services that do not improve health outcomes or are otherwise ineffective.⁸¹ Coverage decisions send strong incentive signals and thus, are another policy tool - albeit a potentially precarious one - to promote beneficial use of prescription medical products and guard against inappropriate use.⁸² Yet, the political sensitivity regarding cost containment and potential healthcare rationing has prevented the CMS from pursuing more aggressive use of evidence derived via comparative effectiveness analyses to inform coverage decisions. Congressional calls to develop comparative effectiveness evidence have been accompanied by requirements to sever any links to coverage decisions.⁸³ Most recently, an April 2009 amendment to the budget bill in the Senate barely failed that would have explicitly "prohibit[ed] the use of data obtained from comparative effectiveness research to deny coverage of items or services under Federal health care programs."⁸⁴ Ironically, Congress has instructed the public health agencies to develop a research infrastructure

⁸⁰ See Carnahan, *Medicare's Coverage with Study Participation Policy: Clinical Trials Or Tribulations?*, 243-258, *supra* at note 75; Kinney, *Medicare Coverage Decision-Making and Appeal Procedures: Can Process Meet the Challenge of New Medical Technology?*, 1471-1482, *supra* at note 78; and S. B. Foote, "Why Medicare Cannot Promulgate a National Coverage Rule: A Case of Regula Mortis," *Journal of Health Politics, Policy and Law* 27, no. 5 (October 2002), 707-730.

⁸¹ Tunis, *Why Medicare has Not Established Criteria for Coverage Decisions*, 2197, *supra* at note 77... "Using cost-effectiveness analysis for such [coverage] decisions implies that a clinical benefit will not be available because of cost, which is considerably more difficult to justify than a decision not to provide a service because the risks are expected to outweigh the benefits."

⁸² For example, CMS's decision to narrow coverage of erythropoiesis-stimulating agents (ESAs) was a response to overuse and new toxicity data. See Centers for Medicare and Medicaid Services, "Decision Memo for Erythropoiesis Stimulating Agents (ESAs) for Non-Renal Disease Indications (CAG-00383N)," CMS, <http://www.cms.hhs.gov/mcd/viewdecisionmemo.asp?id=203>. The decision was highly controversial - generating more than 2000 comments - both because ESAs are notoriously expensive and the CMS appeared to be more stringent than the FDA. See analysis in P. B. Bach, "Limits on Medicare's Ability to Control Rising Spending on Cancer Drugs," *The New England Journal of Medicine* 360, no. 6 (Feb 5, 2009), 626-633; R. Steinbrook, "Erythropoietin, the FDA, and Oncology," *The New England Journal of Medicine* 356, no. 24 (Jun 14, 2007), 2448-2451.

⁸³ Sec. 1013(d): Research on Outcomes of Health Care Items and Services of *Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Public Law 108-173*... "The Administrator of the Centers for Medicare & Medicaid Services may not use data obtained in accordance with this section to withhold coverage of a prescription drug." Also, Sec. 804: Federal Coordination Council for Comparative Effectiveness Research in *American Recovery and Reinvestment Act of 2009, Public Law 111-5*... "None of the reports submitted under this section or recommendations made by the [Federal Coordinating Council for Comparative Effectiveness Research] shall be construed as mandates or clinical guidelines for payment, coverage, or treatment."

⁸⁴ See U.S. Senate, "U.S. Senate Roll Call Votes 111th Congress - 1st Session: Vote Summary on the Amendment (Kyl Amdt. no.7893)," U.S. Senate, http://www.senate.gov/legislative/LIS/roll_call_lists/roll_call_vote_cfm.cfm?congress=111&session=1&vote=00127 (accessed April 14, 2009). The vote was 44-54 along party lines.

whereby evidence will be developed that will surely create some "losers," and yet, the CMS is not permitted to act on that evidence, which may reduce the chance that patients receive inappropriate treatments.

Similarly, states have mandated coverage for off-label uses of prescription medical products if such off-label use can be supported in the literature or appears in a recognized drug compendia.⁸⁵ These criteria are notably broad and open to interpretation. Most importantly, both the medical literature⁸⁶ and the private drug compendia organizations⁸⁷ have been shown to be subject to bias and undue influence from industry. Thus, these state-specific policies *ensure coverage* despite the fact that off-label uses have not been submitted for formal FDA review and the evidence base on such uses is highly varied and subject to manipulation.

Like the FDA, the CMS struggles to balance the needs of the collective versus the individual. The American public wants the CMS to collectively reimburse services that are safe and effective, however, the individual American does not want to encounter rationing in fulfilling his/her healthcare needs.⁸⁸ While the CMS states that NCDs do not direct physicians regarding the provision of any particular item or service⁸⁹ and the Social Security Amendments of 1965 state "Nothing in this title shall be construed to authorize any Federal officer or employee to exercise any supervision or control over the

⁸⁵ Bach, *Limits on Medicare's Ability to Control Rising Spending on Cancer Drugs*, 631, *supra* at note 82.

⁸⁶ K. Lee, P. Bacchetti and I. Sim, "Publication of Clinical Trials Supporting Successful New Drug Applications: A Literature Analysis," *PLoS Medicine* 5, no. 9 (Sep 23, 2008), e191; K. Rising, P. Bacchetti and L. Bero, "Reporting Bias in Drug Trials Submitted to the Food and Drug Administration: Review of Publication and Presentation," *PLoS Medicine* 5, no. 11 (Nov 25, 2008), e217; discussion e217.

⁸⁷ A. P. Abernethy and others, "Systematic Review: Reliability of Compendia Methods for Off-Label Oncology Indications," *Annals of Internal Medicine* 150, no. 5 (Mar 3, 2009), 341... "Cited evidence was scanty and inconsistent across compendia, which raises questions about the processes by which evidence is identified and selected to generate recommendations, the potential biases or conflicts of interest that affect decisions of whether to include an indication or how to present the evidence, and the comprehensiveness and quality of the evidence that the compendia include." See also Merrill Goozner, "Cancer Compendia and the Potential Over-use and Abuse of Anti-Cancer Drugs," www.gooznews.com, January 27, 2009, <http://www.gooznews.com/archives/001312.html>; and Reed Abelson and Andrew Pollack, "Medicare Widens Drugs it Accepts for Cancer Care," *The New York Times*, sec. A, January 27, 2009. Both report on direct conflicts of interest when companies pay private foundations for their evidence to be reviewed.

⁸⁸ Tunis, *Why Medicare has Not Established Criteria for Coverage Decisions*, 2197, *supra* at note 77, "The tension between population-at-large perspective inherent in coverage decisions and the individual-patient perspective intrinsic to clinical practice is highlighted in each discussion of the criteria to be applied to coverage policy."

⁸⁹ Centers for Medicare and Medicaid Services, *Decision Memo for Erythropoiesis Stimulating Agents (ESAs) for Non-Renal Disease Indications (CAG-00383N)*, *supra* at note 82.

practice of medicine or the manner in which medical services are provided,"⁹⁰ the truth is that *any* limitations in coverage affect access, inevitably upsetting some providers.⁹¹

Healthcare providers are trained to make therapeutic choices based on the risks and benefits of medical products for their individual patients, and may resent a lack of choices because a therapy is too risky or uncertain on a collective scale. When the FDA first began to remove certain drugs from the market in the late 1960s for a lack of showing of efficacy, physicians sued the FDA to enjoin action against the removal.⁹² Later attempts by the FDA to devise a "third way" to manage risk – by allowing products on the market but restricting the rules for their use - was generally opposed by physicians, stating

"limited distribution of any and all drugs to certain classes or subgroups of physicians represents an unwarranted and dangerous intrusion into the ability of the medical profession to provide medical care in a rational manner and eventually develop appreciation for unanticipated efficacy and toxicity."⁹³

However, mere information generation and dissemination of clinical practice guidelines is insufficient to change physician behavior.⁹⁴ Provider resistance to

⁹⁰ Sec. 1801: Prohibition Against any Federal Interference in *Social Security Amendments of 1965, Public Law 89-97*, codified at 42 U.S.C. § 1395.

⁹¹ Tunis, *Why Medicare has Not Established Criteria for Coverage Decisions*, 2196, *supra* at note 77... "Coverage decisions concerning medical necessity made by payers are inevitably resented when they prevent payment for a medical service that a patient and a physician have concluded is desirable."

⁹² See *Forsham v. Califano*, Civil Action No. 77-1478, 442 (United States District Court for the District of Columbia 1977)... suing to prevent the removal of a diabetes drug from the market; *American Pharmaceutical Asso. v. Weinberger*, Civ. A. No. 1485-73, 377 (United States District Court for the District of Columbia 1974)... challenging FDA's regulation limited distribution program methadone; and *Ass'n of Am., Physicians & Surgeons, Inc. v. United States FDA*, Civil Action 00-02898 (HHK), 226 (United States District Court for the District of Columbia 2002)... challenging the FDA's rule requiring studies of drugs in pediatric populations as a condition of approval.

⁹³ Letter from Kenneth L. Melmon, MD to Senator Kennedy dated Apr 5, 1976 in U.S. Department of Health Education and Welfare and Review Panel on New Drug Regulation, *Interim Report: Expansion of FDA Statutory Authority in the Post-Marketing Period for New Drugs* (Washington, DC: DHEW, 1977), 9. The letter was in response to new drug reform legislation, which would have strengthened the FDA's ability to restrict access to prescription medical products. The protested rulemaking was Food and Drug Administration and Department of Health, Education, and Welfare, "Legal Status of Approved Labeling for Prescription Drugs; Prescribing for Uses Unapproved by the Food and Drug Administration (Notice of Proposed Rulemaking)," *Federal Register* 37, no. 158 (August 15, 1972), 16503-16505. See commentary in Kessler, *Regulating the Prescribing of Human Drugs for Nonapproved Uses Under the Food, Drug, and Cosmetic Act*, 693-760, *supra* at note 71; and Sidney A. Shapiro, "Limiting Physician Freedom to Prescribe a Drug for any Purpose: The Need for FDA Regulation," *Northwestern University Law Review* 73 (1978), 801-872.

⁹⁴ For example, see R. Mangione-Smith and others, "The Quality of Ambulatory Care Delivered to Children in the United States," *The New England Journal of Medicine* 357, no. 15 (Oct 11, 2007), 1515-1523; E. A. McGlynn and others, "The Quality of Health Care Delivered to Adults in the United States,"

implementation of evidence-based medicine (EBM) bears out this finding.⁹⁵ Aside from its perceived affront to autonomy, some providers view EBM as merely dressed-up cost containment.⁹⁶ However, generally, physicians have been shown to change their behavior and adopt evidence-based practices in response to financial incentives such as adjusted reimbursement rates⁹⁷; administrative/penal incentives such as utilization review and prior authorization⁹⁸; and peer pressure⁹⁹.

Whether because of the loss of treatment options (e.g., withdrawals of misused prescription medical products) or the greater trend toward EBM, there has been greater tolerance of prescribing restrictions in recent years. For instance, the FDA initiated four different risk management phases to its Accutane™ (isotretinoin) campaign, a medication for severe acne with teratogenic side effects. With each phase, the FDA escalated restrictions on use including a move away from information-based campaigns and toward restricted distribution with mandatory compliance to reduce exposed pregnancy rates.¹⁰⁰ This escalation illustrates both the FDA's initial attempts to act in the least restrictive manner, and its eventual realization of the inadequacy of policies that rely on passive

The New England Journal of Medicine 348, no. 26 (Jun 26, 2003), 2635-2645. See also extensive analysis in U.S. Office of Technology Assessment, *Identifying Health Technologies that Work: Searching for Evidence*, 173-198, *supra* at note 30.

⁹⁵ See S. C. Mathews and P. J. Pronovost, "Physician Autonomy and Informed Decision Making: Finding the Balance for Patient Safety and Quality," *Journal of the American Medical Association* 300, no. 24 (Dec 24, 2008), 2913-2915; and S. M. Shortell, T. G. Rundall and J. Hsu, "Improving Patient Care by Linking Evidence-Based Medicine and Evidence-Based Management," *Journal of the American Medical Association* 298, no. 6 (Aug 8, 2007), 674... "There are substantial, similar barriers to evidence use: time pressures, perceived threats to autonomy, the preference for 'colloquial' knowledge based on individual experiences, difficulty in accessing the evidence base, difficulty differentiating useful and accurate evidence from that which is inaccurate or inapplicable, and lack of resources."

⁹⁶ D. L. Sackett and others, "Evidence Based Medicine: What it Is and What it Isn't," *British Medical Journal* 312, no. 7023 (Jan 13, 1996), 72... responding to early criticisms that EBM was "hijacked by purchasers and managers to cut the costs of health care. This would not only be a misuse of evidence based medicine but suggests a fundamental misunderstanding of its financial consequences. Doctors practising evidence based medicine will identify and apply the most efficacious interventions to maximise the quality and quantity of life for individual patients; this may raise rather than lower the cost of their care."

⁹⁷ A. M. Epstein, T. H. Lee and M. B. Hamel, "Paying Physicians for High-Quality Care," *The New England Journal of Medicine* 350, no. 4 (Jan 22, 2004), 406-410.

⁹⁸ Kris Hundley, "Approval Process Lower the Number of Kids on Atypical Prescriptions," *The St. Petersburg Times*, sec. A, March 29, 2009. Prior authorization policies designed to reduce unnecessary utilization may also inadvertently reduce necessary utilization. For example, see C. A. Jackevicius and others, "Cardiovascular Outcomes After a Change in Prescription Policy for Clopidogrel," *The New England Journal of Medicine* 359, no. 17 (Oct 23, 2008), 1802-1810.

⁹⁹ U.S. Office of Technology Assessment, *Identifying Health Technologies that Work: Searching for Evidence*, 181-186, *supra* at note 30.

¹⁰⁰ L. Abroms and others, "What is the Best Approach to Reducing Birth Defects Associated with Isotretinoin?" *PLoS Medicine* 3, no. 11 (Nov, 2006), e483.

information dissemination without accompanying system-level mechanisms to stimulate behavioral change. From a risk management perspective, much time and effort has been lost waiting for popular conformance to emergent norms.

Therefore, in addition to building public health information infrastructure that collects emerging postmarket data and generates actionable decision criteria, policy innovations must *manage* and *communicate* the dynamic states of information so that stakeholders strive to advance beneficial use and prevent or mitigate inappropriate use (i.e., contraindicated uses). Desired outcomes are achievable only if these stakeholders are motivated and capable of altering their behavior in light of the new information.¹⁰¹ Thus, policy innovations must also seek to motivate behavioral change with system-level incentives built to enhance the ability of healthcare providers to deliver the right products to the right people in the right dosage at the right time.

¹⁰¹ *ibid.*

II. Historical Context

This chapter traces the broad contextual factors that have contributed to the current state of incomplete and imperfect information on prescription medical products in addition to highlighting the consequences of inappropriate risk management. Our arrival at the current state is not a mystery. Rather, it is the confluence of powerful interest groups, incredible advances in science and medicine, and the uniquely American healthcare system. The specific historical policies that have been employed to generate postmarket data and manage it will be reviewed in the next chapter.

A. *Overall Differences in the Speed of Innovation*

Significant financial, technical, scientific, and academic resources have yielded more abundant and varied medical products in the last seventy years. These products have a high degree of technical and scientific complexity, require intensive research and development efforts, and dramatically and personally affect the health and welfare of millions. Public funding, funneled through the NIH, has supported much of the significant progress in this field.¹⁰² Private investment is also substantial and largely responsible for developing scientific and technical research into useful medical products (i.e. translating from the bench to the bedside).¹⁰³ Lastly, the passage of the Bayh-Dole Act in 1980 further demonstrates the government's considerable interest in ensuring that federally funded research efforts result in commercially available medical technologies.¹⁰⁴ However, this resource intensity typically drops off sharply at the time of marketing despite the fact that much of the relevant information to promote safe and

¹⁰² See Ron Bouchard, "Balancing Public and Private Interests in the Commercialization of Publicly Funded Medical Research: Is there a Role for Compulsory Government Royalty Fees?" *Boston University Journal of Science and Technology Law* 13 (Summer 2007), footnote 116, citing 1) National Institutes of Health, NIH Contributions to Pharmaceutical Development (Feb. 2000); and Iain Cockburn, Rebecca Henderson and National Bureau of Economic Research, *Public-Private Interaction and the Productivity of Pharmaceutical Research*, no. 6018 (Cambridge, MA: National Bureau of Economic Research, 1997).

¹⁰³ Benjamin Zycher, Joseph A. DiMasi and Christopher-Paul Milne, *The Truth about Drug Innovation: Thirty-Five Summary Case Histories on Private Sector Contributions to Pharmaceutical Science*, Medical Progress Report No. 6 (New York, NY: Manhattan Institute, 2008), http://www.manhattan-institute.org/pdf/mprr_06.pdf (accessed January 20, 2009).

¹⁰⁴ *Bayh-Dole University and Small Business Patent Procedures Act of December 12, 1980*, Public Law 96-517, *Statutes at Large* 94 (December 12, 1980), 3015-3028.

effective use is yet unknown.¹⁰⁵ Simply put, public and private support for drug development dramatically expanded utilization of pharmaceuticals as the preferred mode of therapeutic intervention. It did so without commensurate levels of financial, technical, scientific, and academic attention to innovations in pharmacoepidemiology and outcomes research that are necessary to safely absorb the effects of such expansion. The heavy U.S. investment in biomedical research has been both a blessing and a curse, and is an excellent example of unplanned system-level effects that result from policy interventions.¹⁰⁶ Incredible scientific and medical advances have begat innovative and promising prescription medical products, but as a society, we have failed in planning for a comprehensive means to evaluate the benefits and risks of these technologies in comparison to alternatives. One academic noted:

"Pharmacoepidemiology is still in its adolescence... We forgot how difficult it was to establish the rules of the road for conducting randomized trials. In terms of design theory and public policy, drug-epidemiology research is now where randomized trials were in the 1950s."¹⁰⁷

In general, healthcare stakeholders still struggle with what types of data to collect, the manner in which they should be collected, the methodologies that should be used to analyze them, and the reliability of such analyses for public health decision criteria.¹⁰⁸

B. Chloramphenicol: Early Evidence of Postmarket Problems

In the 1950s, the government's early experiences with the antibiotic chloramphenicol demonstrated emerging problems with prescription medical products that presented complicated benefit-risk profiles *only after use in the postmarket environment*. Spontaneous clinical reports of rare blood disorders associated with the drug began to come to the FDA in the form of anecdotal clinical reports of "drug

¹⁰⁵ Institute of Medicine (IOM), *The Future of Drug Safety: Promoting and Protecting the Health of the Public*, 193-204, *supra* at note 15; U.S. Government Accountability Office, *Improvement Needed in FDA's Postmarket Decision-Making and Oversight Process*, 12-16, 28-29, 34-36, *supra* at note 15; S. Hennessy and B. L. Strom, "PDUFA Reauthorization--Drug Safety's Golden Moment of Opportunity?" *The New England Journal of Medicine* 356, no. 17 (Apr 26, 2007), 1703-1704.

¹⁰⁶ John Sterman, *Business Dynamics: Systems Thinking and Modeling for a Complex World* (Boston: Irwin/McGraw-Hill, 2000), 10-11. Sterman refers to this phenomenon as policy resistance, which arises "when we do not understand the full range of feedbacks operating in the system."

¹⁰⁷ J. Avorn, "In Defense of Pharmacoepidemiology--Embracing the Yin and Yang of Drug Research," *The New England Journal of Medicine* 357, no. 22 (Nov 29, 2007), 2221.

¹⁰⁸ Strom, *Methodologic Challenges to Studying Patient Safety and Comparative Effectiveness*, S15, *supra* at note 12, "Addressing these issues will require novel research approaches such as new study designs, innovative risk-adjustment methods to control for confounding, active surveillance of adverse effects, and new ways to [achieve] bias reduction in observational studies."

experience."¹⁰⁹ On the advice of an external expert panel, the FDA attempted to persuade Parke, Davis (the sponsor) to strengthen the safety risk information in direct mailings, journal advertising, and sales calls to reduce the number of adverse reports.¹¹⁰ The agency's intentions largely went unheeded because it was unable to enforce them, and in some cases, the agency was openly contravened.¹¹¹ The FDA continued to receive information that the drug was over-prescribed for trivial infections such as colds and other minor infections that could be treated with less risky antibiotics.¹¹² In short, all efforts to limit misuse fell short.

Nearly ten years later, the Kefauver-Harris Amendments in 1962 gave the FDA increased statutory authority to ensure side effects and warnings were included in the manufacturer's advertising.¹¹³ Still, chloramphenicol use was rising, and frustration with the FDA led the California Senate to hold hearings and considering passing a bill that would limit prescribing.¹¹⁴ The FDA found itself in a very poor position. Its only leverage was withdrawal of the drug, a less than ideal solution since it was the best course of therapy for three life-threatening infections.¹¹⁵ However, the changes to the label had

¹⁰⁹ Reidenberg, *Improving How we Evaluate the Toxicity of Approved Drugs*, 2, *supra* at note 52, citing R. O. Wallerstein and others, "Statewide Study of Chloramphenicol Therapy and Fatal Aplastic Anemia," *Journal of the American Medical Association* 208, no. 11 (Jun 16, 1969), 2045-2050.

¹¹⁰ Testimony of Herbert L. Ley in U.S. House Committee on Government Operations, *Drug Efficacy, Part 1*, 91st Cong., 1st sess., 1970, 6. The letter to the FDA from the National Research Council panel available in U.S. Senate Committee on the Judiciary, *Administered Prices in the Drug Industry (Antibiotics -- Appendix B)*, Part 26, 86th Cong., 2d sess., 1973, 15833.

¹¹¹ Hilts, *Protecting America's Health: The FDA, Business, and One Hundred Years of Regulation*, 111-115, *supra* at 65; Testimony of Herbert L. Ley in U.S. House Committee on Government Operations and Intergovernmental Relations Subcommittee, *Drug Efficacy, Part 1*, 6-11, *supra* at note 110; Testimony of Harry Loynd in U.S. Senate Committee on the Judiciary, *Administered Prices in the Drug Industry (Antibiotics)*, Part 24, 86th Cong., 2d sess., 1973, 12988-13989, 13996-14040, 14051-14075; Testimony of James T. Weston in U.S. Senate Select Committee on Small Business, *Competitive Problems in the Drug Industry, Part 6*, 90th Cong., 1st and 2d sess., 1969, 2472-2479.

¹¹² See National Academy of Sciences, National Research Council, *Report of the Special Advisory Committee to the Secretary of Health, Education, and Welfare to Review the Policies, Procedures, and Decisions of the Division of Antibiotics and the New Drug Branch of the Food and Drug Administration* (Washington, DC: National Academy of Sciences, 1960); Testimony of James T. Weston in U.S. Senate Select Committee on Small Business and Subcommittee on Antitrust and Monopoly, *Competitive Problems in the Drug Industry, Part 6*, 2480-2496, *supra* at note 111.

¹¹³ Sec. 131: Prescription Drug Advertisements in *Drug Amendments of 1962, Public Law 87-781*, codified at 21 U.S.C. § 352(n).

¹¹⁴ Testimony of Edgar F. Elfstrom and James T. Goddard in U.S. Senate Select Committee on Small Business and Subcommittee on Antitrust and Monopoly, *Competitive Problems in the Drug Industry, Part 6*, 2573, 2629, 2636, 2639, *supra* at note 111.

¹¹⁵ Congressional Research Service, Irene Jillson and Vikki A. Zegel, *Competitive Problems in the Drug Industry* (Washington, DC: U.S. Government Printing Office, 1979), 15-20... Three conditions calling for the use of chloramphenicol were mentioned by various witnesses at the hearings. These were: (1) Typhoid;

proved largely ineffective in preventing adverse drug events from improper use. In Congressional testimony, the FDA Commissioner testified:

"[A tougher warning] does no good. I cannot tell you that this new warning is going to do any good. I can tell you the new warning, plus the 'Dear Doctor' letter we intend to send to every doctor and hospital administrator, plus the material we are going to provide the publishers of medical magazines and newspapers, plus the constant review on the monthly production data [the amount of chloramphenicol certified], and the rewarning of the profession when it indicates any upswing, plus the change in the reminder ads - these represent what we in our opinion feel we can do now within our present authority."¹¹⁶

Historian Thomas Maeder noted that despite the deaths, lawsuits, FDA actions, and Congressional hearings, physicians changed their practice patterns in large part because Parke, Davis's patent expired in 1967 and they stopped heavy physician promotion of the product.¹¹⁷ The FDA had clearly failed to ensure that the available information was well-comprehended by providers and it could not outcompete the manufacturer's resources and intentions.

C. Increasing Complexity of Disease States and their Treatments

In the 1970s, Levodopa, a breakthrough treatment for Parkinson's disease, was the first prescription medical product approved with significant postmarket evidence generation commitments. There was indication that the drug posed serious safety hazards, and long-term animal toxicity studies were not complete.¹¹⁸ However, with no treatment available to patients, it offered significant therapeutic benefit, and was lobbied for by patient groups.¹¹⁹ The FDA approved it for use prior to completion of the associated animal studies with several conditions, one of which was a first-of-its-kind postmarket study.¹²⁰

The Levodopa regulations were the first acknowledgement of the need for long-term evidence generation and assessment, particularly for drugs that would be taken by

(2) severe salmonellosis; and (3) II. Influenzae meningitis.

¹¹⁶ Testimony of James L. Goddard in U.S. Senate Select Committee on Small Business and Subcommittee on Antitrust and Monopoly, *Competitive Problems in the Drug Industry, Part 6*, 2644, *supra* at note 111.

¹¹⁷ Thomas Maeder, *Adverse Reactions*, 1st ed. (New York: Morrow, 1994).

¹¹⁸ Charles Steenburg, "The Food and Drug Administration's Use of Postmarketing (Phase IV) Study Requirements: Exception to the Rule?" *Food and Drug Law Journal* 61 (2006), 301.

¹¹⁹ *ibid.*, 301; U.S. House Committee on Government Operations, *Regulatory Policies of the Food and Drug Administration*, 91st Cong., 2nd sess., 1971, 16-17.

¹²⁰ Food and Drug Administration and Department of Health, Education, and Welfare, "Approved New Drugs that Require Continuation of Long-Term Studies, Records, and Reports; Listing of Levodopa," *Federal Register* 37, no. 4 (January 7, 1972), 201-202.

patients chronically for the rest of their lives.¹²¹ The harm of exposure to unknown side effects had to be balanced against the harm that might occur to patients in the interim period if no drug was offered to them at all. In 1977, the Review Panel on New Drug Regulation recommended giving the FDA greater statutory authority in the postmarket environment, specifically the ability to require postapproval clinical trials to study longitudinal effects on drugs.¹²² It reasoned that if the FDA were able to conditionally approve drugs based on the promise of forthcoming information, then reviewers would feel more comfortable in approving a drug at an earlier stage, particularly if there was a strong case for the potential benefits as with Levodopa.

Multiple bills were introduced into Congress to strengthen this part of the FDA's authority, including a Carter Administration Bill that would have allowed the FDA to require drug sponsors to maintain active postmarket surveillance databases on their products as well as to conduct postapproval studies when adverse effects or a lack of efficacy was suspected.¹²³ Four of these bills died in committee and only Senator Edward Kennedy's 1979 Drug Regulation Reform Act passed a single house of Congress.¹²⁴ Notably, this bill allowed for limited distribution for drugs that could not meet the normal standards for safety and efficacy; and second, the bill called for a less stringent evidence standard for immediate withdrawal of drugs from the market.¹²⁵

Like Levodopa, the onset of the AIDS crisis (and the consequent rise of patient advocacy groups) drew more attention to the harm caused by delays in approving new drug therapies for desperately ill individuals.¹²⁶ Again, postmarket surveillance tools were used to justify more rapid premarket approval processes based on less data (e.g., little or no confirmatory Phase III or IV studies) or by applying a different evidentiary

¹²¹ *ibid.*, 201... "A majority of the comments [received in response to the proposed rulemaking] agreed that in exceptional cases the benefit to the public would warrant approval of a new-drug application on condition that necessary long-term studies would be conducted."

¹²² Institute of Medicine (IOM), *The Future of Drug Safety: Promoting and Protecting the Health of the Public*, 156, *supra* at note 15.

¹²³ Steenburg, *The Food and Drug Administration's Use of Postmarketing (Phase IV) Study Requirements: Exception to the Rule?*, 313, *supra* at note 118.

¹²⁴ Institute of Medicine (IOM), *The Future of Drug Safety: Promoting and Protecting the Health of the Public*, 156, *supra* at note 15.

¹²⁵ U.S. Office of Technology Assessment, *Postmarketing Surveillance of Prescription Drugs*, 26, *supra* at note 19.

¹²⁶ Institute of Medicine (IOM), *The Future of Drug Safety: Promoting and Protecting the Health of the Public*, 75, *supra* at note 15.

standard for that data. Two mechanisms were introduced through informal rulemaking procedures (as opposed to statutory changes): "fast track" (Subpart E) rules¹²⁷ and "accelerated approval" (Subpart H) rules¹²⁸. These administrative law options were attempts to compress the drug development cycle for medications that addressed unmet needs for patients with "severely-debilitating" or "immediately" life-threatening illnesses (e.g. AIDS or cancer). Specifically, Subpart E and Subpart H rules could be invoked to deliver drugs to patients concurrent with premarket trials instead of following their completion. While the FDA went to extreme lengths to emphasize that the new procedures did not reflect reduced standards of evidence, they also were quick to point out that the target population was willing to accept greater risks from their medications in light of the severity of medical conditions.¹²⁹ These administrative policy options evolved as a means to manage prescription medical products that were designed to treat increasingly complicated disease states.

D. The Prescription Drug User Fee Act: A Shift Away from the Postmarket

In 1992, the FDA and industry representatives negotiated the Prescription Drug User Fee Act (PDUFA). PDUFA supplemented the FDA's budget by collecting fees from the pharmaceutical and biotechnology industries that would be used toward new drug and biologics approval review processes.¹³⁰ The fees allowed the FDA to hire significantly more personnel (more than 1000 full-time equivalents during PDUFA I¹³¹) into the agency for new drug review purposes, and, in exchange, the FDA agreed to set performance goals which translated into deadlines for new drug application (NDA)

¹²⁷ Food and Drug Administration and Department of Health and Human Services, "Investigational New Drug, Antibiotics, and Biological Drug Product Regulations; Procedures for Drugs Intended to Treat Life-Threatening and Severely Debilitating Illnesses." *Federal Register* 53, no. 204 (October 21, 1988), 41516-41524.

¹²⁸ Food and Drug Administration and Department of Health and Human Services, "New Drug, Antibiotic, and Biological Drug Product Regulations; Accelerated Approval," *Federal Register* 57, no. 239 (December 11, 1992), 58942-58960.

¹²⁹ *ibid.*, 58944, *supra* at note 128... "Approval under this rule requires, therefore, that the effect shown be, in the judgment of the agency, clinically meaningful, and of such importance as to outweigh the risks of treatment. This judgment does not represent either a 'lower standard' or one inconsistent with section 505(d) of the act, but rather an assessment about whether different types of data show that the same statutory standard has been met."

¹³⁰ "The Prescription Drug User Fee Act of 1992, Public Law 102-571," *Statutes at Large* 106 (October 29, 1992), 4491-4505, codified at 21 U.S.C. § 379(g). The 1992 version is known as PDUFA I. It has been updated every five years and each renewal cycle is noted with a subsequent Roman numeral.

¹³¹ Institute of Medicine (IOM), *The Future of Drug Safety: Promoting and Protecting the Health of the Public*, 195, *supra* at note 15.

reviews. PDUFA I dramatically decreased review times for NDAs. The GAO reported that the median approval time for standard drugs (i.e., those not designated as priority or qualifying for Subpart E or H programs) was 27 months in 1993 and 14 months by 2001.¹³²

The speed of drug approvals required under the PDUFA scheme made the American market the first market for initial approval for the first time since the Kefauver-Harris Drug Amendments were enacted.¹³³ In 1988, the FDA was the first agency to grant approval four percent of the time, a figure that had risen to 68% ten years later after PDUFA had been in place nearly five years.¹³⁴ Therefore, drug safety problems that were once discovered overseas first were now apparent in the U.S. first, and the postmarket divisions were under-prepared to deal with the rise in first-discovery adverse drug reactions.¹³⁵ Further, the FDA could no longer rely on the foreign data to guide approval decisions; this was a marked change from a time when several harmful drugs first available in Europe were kept out of the U.S. market entirely in the pre-PDUFA era.¹³⁶

At the same time, just a few years prior to PDUFA I's enactment, the GAO released a report on the likelihood of discovering serious risks of adverse drug reactions (e.g., hospitalization, death, permanent disability) in the postmarket approval period. They found such risks in 51.5% of drugs approved at that time.¹³⁷ Thus, with evidence that a high probability existed for safety concerns to arise postapproval, it was particularly significant that the largest number of novel drugs reached the market at a time when PDUFA fees were unavailable for postmarket epidemiology activities. On the

¹³² U.S. General Accounting Office, *Food and Drug Administration: Effect of User Fees on Drug Approval Times, Withdrawals, and Other Agency Activities*, GAO-02-958 (Washington, DC: GPO, 2002), 8, <http://www.gao.gov/new.items/d02958.pdf>.

¹³³ See U.S. General Accounting Office, *FDA Drug Approval: A Lengthy Process that Delays the Availability of Important New Drugs*, 83, *supra* at note 21, criticizing the "drug lag" in America relative to other nations. Also, see Friedman and others, *The Safety of Newly Approved Medicines: Do Recent Market Removals Mean there is a Problem?*, 1732, *supra* at note 15.

¹³⁴ Steenburg, *The Food and Drug Administration's Use of Postmarketing (Phase IV) Study Requirements: Exception to the Rule?*, 324, *supra* at note 118; Friedman and others, *The Safety of Newly Approved Medicines: Do Recent Market Removals Mean there is a Problem?*, Figure 5 on 1733, *supra* at note 15.

¹³⁵ Steenburg, *The Food and Drug Administration's Use of Postmarketing (Phase IV) Study Requirements: Exception to the Rule?*, 299, *supra* at note 118; Okie, *Safety in Numbers--Monitoring Risk in Approved Drugs*, 1173-1174, *supra* at note 10; Wood, Stein and Woosley, *Making Medicines Safer--the Need for an Independent Drug Safety Board*, 1851-1854, *supra* at note 52.

¹³⁶ Friedman and others, *The Safety of Newly Approved Medicines: Do Recent Market Removals Mean there is a Problem?*, 1731, *supra* at note 15.

¹³⁷ U.S. General Accounting Office, *FDA Drug Review: Postapproval Risks, 1976-85*, 3, *supra* at note 5.

whole, the use of pharmaceuticals was on the rise.¹³⁸ The GAO reported that pharmacists dispensed 3.1 billion prescriptions in the U.S. in 2001 compared to 1.9 billion in 1992 and 2.4 billion in 1997.¹³⁹

Systemic effects of the user fee structure exacerbated the FDA's ability to cope with a flood of new prescription medical products and their consequent undiscovered adverse reactions. User fees, by agreement, could *only be collected* if minimum staffing and government appropriations in the drug review divisions were maintained.¹⁴⁰ To ensure collection, the FDA transferred personnel to the drug review divisions at the expense of other functions such as postmarket epidemiology.¹⁴¹ Also, the sunset provision of PDUFA put the FDA in the unenviable situation of having to renegotiate performance goals (usually more taxing) every five years or risk firing a majority of its staff if user fees were not renewed.¹⁴²

A record five drugs were withdrawn from the market due to serious adverse reactions between 1997-1998, three of which were on the market for less than two years and had been approved during the PDUFA I period.¹⁴³ Thus, when PDUFA III was reauthorized in 2002, critics insisted that user fees should be allowed for "strengthening and improving the review and monitoring of drug safety."¹⁴⁴ However, it was not without limit. The FDA was to implement review and monitoring by "collecting, developing, and reviewing safety information on the drugs, including adverse event reports" for *up to three years* after they were approved.¹⁴⁵ Given that a study released five months earlier

¹³⁸ James L. Zelenay Jr, "The Prescription Drug User Fee Act: Is a Faster Food and Drug Administration always a Better Food and Drug Administration?" *Food and Drug Law Journal* 60 (2005), 321, noting that the increase was augmented by an unprecedented level of spending on DTCA, which quadrupled between 1994 and 1999.

¹³⁹ U.S. General Accounting Office, *Food and Drug Administration: Effect of User Fees on Drug Approval Times, Withdrawals, and Other Agency Activities*, 5, *supra* at note 132, quoting National Institute of Health Care Management.

¹⁴⁰ B. N. Kuhlik, "Industry Funding of Improvements in the FDA's New Drug Approval Process: The Prescription Drug User Fee Act of 1992," *Food and Drug Law Journal* 47 (1992), 500.

¹⁴¹ U.S. General Accounting Office, *Food and Drug Administration: Effect of User Fees on Drug Approval Times, Withdrawals, and Other Agency Activities*, 14-27, *supra* at note 132.

¹⁴² Zelenay, *The Prescription Drug User Fee Act: Is a Faster Food and Drug Administration always a Better Food and Drug Administration?*, 330,337, *supra* at note 138.

¹⁴³ Friedman and others, *The Safety of Newly Approved Medicines: Do Recent Market Removals Mean there is a Problem?*, 1728-1734, *supra* at note 15.

¹⁴⁴ Sec. 502(3)(B): Findings in *Title V: Prescription Drug User Fee Amendments of 2002*, Public Law 107-188, *Statutes at Large* 116 (June 12, 2002, 2002), 687-697.

¹⁴⁵ Sec. 503: Definitions in *Title V: Prescription Drug User Fee Amendments of 2002*, Public Law 107-188, codified at 21 U.S.C. § 379(g)(6)(F).

found that only half of serious adverse drug reactions were discovered in the *first seven years* on the market, the additional monies from industry were more a gesture than an indication that true paradigm shifts were coming.¹⁴⁶ In fact, a later FDA study found multiple safety-related label changes occurred as long as thirteen years after initial approval.¹⁴⁷

E. Rising Cost of Healthcare, Quality Concerns Drive Evidence-based Medicine

As briefly discussed in chapter one, soon after the development of the Medicare program, the availability of new medical technologies combined with generous utilization of services contributed to the dramatic rise in healthcare costs.¹⁴⁸ The rate of new medical innovation outpaced the ability to evaluate its usefulness. Various federal technology assessment agencies were developed to generate evidence to influence clinical care.¹⁴⁹ Their shared mission was to develop measures of healthcare value by comparing the clinical effectiveness of various interventions. This initiative was based on the work of Archie Cochrane, a physician and epidemiologist who argued for the elimination of ineffective care through the development of a more substantial evidence base.¹⁵⁰ Additionally, John Wennberg demonstrated high-level geographic variation in utilization rates of various medical practices that were unexplained by differences in patient values or needs.¹⁵¹ Wennberg theorized that geographic variation, and its suggestion of both over- and under-utilization, resulted in inappropriately high costs of care and variable outcomes.

¹⁴⁶ Zelenay, *The Prescription Drug User Fee Act: Is a Faster Food and Drug Administration always a Better Food and Drug Administration?*, 329, *supra* at note 138; Lasser and others, *Timing of New Black Box Warnings and Withdrawals for Prescription Medications*, 2215-2220, *supra* at note 5.

¹⁴⁷ McAdams, *Timing and Characteristics of Safety-Related Actions for New Molecular Entities (1991-2006): A Preliminary Study*, *supra* at note 5.

¹⁴⁸ Kinney, *Medicare Coverage Decision-Making and Appeal Procedures: Can Process Meet the Challenge of New Medical Technology?*, 1467-1469, *supra* at note 78.

¹⁴⁹ For a history of federal efforts, see Eisenberg and Zarin, *Health Technology Assessment in the United States: Past, Present, and Future*, 192-198, *supra* at note 78. Also, see Institute of Medicine (IOM), *Knowing what Works in Health Care: A Roadmap for the Nation*, 26-27, *supra* at note 366.

¹⁵⁰ See U.S. Office of Technology Assessment, *Identifying Health Technologies that Work: Searching for Evidence*, 19, *supra* at note 30, referencing Archibald Leman Cochrane, *Effectiveness and Efficiency: Random Reflections on Health Services* (London: Nuffield Provincial Hospitals Trust, 1972).

¹⁵¹ J. E. Wennberg, "Dealing with Medical Practice Variations: A Proposal for Action," *Health Affairs* 3, no. 2 (Summer 1984), 8... "Some of the differences in opinion arise because the necessary scientific information on outcomes is missing: controversies about alternative therapies cannot be resolved through appeal to existing evidence."

By 1989, the AHCPR, forerunner of the AHRQ, inherited federal technology assessment efforts, and central to its new duties was to promote research on outcomes and to develop clinical practice guidelines.¹⁵² In order to fulfill its mandate, the AHCPR requested the advice of the IOM who noted, "the creation of practice guidelines function...can be seen as part of a significant cultural shift, a move away from unexamined reliance on professional judgment toward more structured support and accountability for such judgment."¹⁵³ These guidelines were one of the hallmarks of the emergence of evidence-based medicine in the 1990s, defined as a practice of "efficient literature searching and the application of formal rules of evidence evaluating the clinical literature."¹⁵⁴ The approach was not taken without reservation that "the evidence might be applied in ways that would limit individuals' choices of medical treatments."¹⁵⁵ While many viewed developments in evidence-based medicine and clinical practice guidelines as rigid rules or "cookbook medicine" that presented challenges to physician autonomy, the authors of the term emphasized the probabilistic aspects of medical decision-making and the need to integrate the best available quantitative studies of evidence with clinical judgment.¹⁵⁶ In fact, it was designed to straddle the fine line between accommodating natural variations in patients and their preferences, and weeding out wasteful treatments.

Synthesis of medical evidence in the form of clinical practice guidelines took root beyond the US government. Non-profit organizations such as the Cochrane Collaboration and the ECRI Institute began similar programs to catalog and publish systematic reviews.¹⁵⁷ Private organizations such as Blue Cross Blue Shield's Technology

¹⁵² Title IX: Agency for Health Care Policy and Research in *Omnibus Budget Reconciliation Act*, Public Law 101-239, *Statutes at Large* 103 (December 19, 1989), 2106-2492... "The purpose of the Agency is to enhance the quality, appropriateness, and effectiveness of health care services." See also Eisenberg and Zarin, *Health Technology Assessment in the United States: Past, Present, and Future*, 192-198, *supra* at note 78.

¹⁵³ Institute of Medicine (IOM), *Clinical Practice Guidelines: Directions for a New Program*, eds. Marilyn J. Field and Kathleen N. Lohr, IOM-90-08 (Washington, D.C.: National Academy Press, 1990), 2.

¹⁵⁴ Evidence-Based Medicine Working Group, "Evidence-Based Medicine. A New Approach to Teaching the Practice of Medicine," *Journal of the American Medical Association* 268, no. 17 (Nov 4, 1992), 2420.

¹⁵⁵ U.S. Office of Technology Assessment, *Identifying Health Technologies that Work: Searching for Evidence*, 1, *supra* at note 30.

¹⁵⁶ See comments in Sackett and others, *Evidence Based Medicine: What it is and What it Isn't*, 71, *supra* at note 96, responding to criticisms that evidence-based medicine is "a dangerous innovation, perpetrated by the arrogant to serve cost cutters and suppress clinical freedom."

¹⁵⁷ Institute of Medicine (IOM), *Crossing the Quality Chasm: A New Health System for the 21st Century* (Washington, D.C.: National Academy Press, 2001), 149-150. See also Institute of Medicine (IOM), *Knowing what Works in Health Care: A Roadmap for the Nation*, 43-44, *supra* at note 366.

Evaluation Center and Hayes Inc, developed health technology assessments for a variety of healthcare organizations, including healthcare plans and hospitals.¹⁵⁸ Also, practicing evidence-based medicine gained momentum when accreditation agencies such as the National Committee on Quality Assurance sought data to measure the quality of healthcare delivered and to certify evidence-based organizations.¹⁵⁹ Quality concerns in the 1990s culminated in two landmark IOM studies that described the harm to patients from medical error, caused in part by incomplete evidence.¹⁶⁰ Both studies recommended the development of public health information infrastructure "so that decisions are based on evidence rather than anecdote."¹⁶¹

Seeking more acceptance among healthcare providers, the federal government removed itself from authoring clinical practice guidelines, and outsourced their development in the late 1990s.¹⁶² Since then, guidelines have grown to number in the thousands in the U.S. and are still associated with cost-control and quality initiatives.¹⁶³ Nonetheless, the IOM found, "developing and disseminating practice guidelines alone has minimal effect on clinical practice."¹⁶⁴ In short, other solutions are needed. The call for evidence-based medicine in clinical practice remains potent albeit slow; the IOM has set the following goal: by 2020, ninety percent of clinical decisions will be supported by accurate timely, and up-to-date clinical information, and will reflect the best available

¹⁵⁸ *ibid.*, 43-44.

¹⁵⁹ *ibid.*, 48.

¹⁶⁰ See Institute of Medicine (IOM), *To Err is Human: Building a Safer Health System* (Washington, DC: National Academy Press, 1999); Institute of Medicine (IOM), *Crossing the Quality Chasm: A New Health System for the 21st Century*, *supra* at note 158.

¹⁶¹ Institute of Medicine (IOM), *To Err is Human: Building a Safer Health System*, 78. See also Chapter 6 of Institute of Medicine (IOM), *Crossing the Quality Chasm: A New Health System for the 21st Century*, 146... "The Secretary of the Department of Health and Human Services should be given the responsibility and necessary resources to establish and maintain a comprehensive program aimed at making scientific evidence more useful and accessible to clinicians and patients."

¹⁶² See Eisenberg, *The Agency for Healthcare Research and Quality: New Challenges, New Opportunities*, xi-xvi, *supra* at note 34.

¹⁶³ S. Timmermans, "From Autonomy to Accountability: The Role of Clinical Practice Guidelines in Professional Power," *Perspectives in Biology and Medicine* 48, no. 4 (Autumn 2005), 491.

¹⁶⁴ Institute of Medicine (IOM), *Crossing the Quality Chasm: A New Health System for the 21st Century*, 151, *supra* at note 157. Empirical studies such as Mangione-Smith and others, *The Quality of Ambulatory Care Delivered to Children in the United States*, 1515-1523, *supra* at note 94; and McGlynn and others, *The Quality of Health Care Delivered to Adults in the United States*, 2635-2645, *supra* at note 94, support such findings.

evidence.¹⁶⁵

F. Drug Safety Crises and New Legislation

The need for better evidence in healthcare delivery was particularly strongly felt in relation to prescription medical products. Litigation against the manufacturers of Paxil™ (paroxetine hydrochloride), Celebrex™ (celecoxib), Baycol™ (cerivastatin), and Vioxx™ (rofecoxib) demonstrated that pharmaceutical companies routinely withheld clinical trial data that resulted in negative outcomes concerning their products.¹⁶⁶ Such masking of evidence creates an incomplete picture for public health agencies and healthcare providers that routinely manage the use of these products. Additionally, Congressional hearings were held on the potentially known but unpublished link between adolescent suicides and anti-depressants¹⁶⁷ and on the failed regulatory response to Vioxx™ (rofecoxib).¹⁶⁸ Shaken confidence in the FDA's ability to manage risks was not limited to academics, policy wonks, and legislators.¹⁶⁹ Many were concerned that user fees were becoming a larger proportion of the FDA's operating budget, creating an unsurmountable conflict of interest.¹⁷⁰ The FDA's own Science and Technology Board reported that consumer confidence in the FDA fell from 80% in the 1970s to 36% in 2006.¹⁷¹ The FDA requested that the IOM investigate and make suggestions to improve

¹⁶⁵ Institute of Medicine (IOM), *Learning Healthcare System Concepts v2008: Annual Report*, iv, *supra* at note 57.

¹⁶⁶ Fontanarosa, Rennie and DeAngelis, *Postmarketing Surveillance--Lack of Vigilance, Lack of Trust*, 2647-2650, *supra* at note 52.

¹⁶⁷ U.S. House Committee on Energy and Commerce and Subcommittee on Oversight and Investigations, *FDA's Role in Protecting the Public Health: Examining FDA's Review of Safety and Efficacy Concerns in Anti-Depressant Use by Children*, *supra* at note 22.

¹⁶⁸ See U.S. Senate Committee on Finance, *FDA, Merck, and Vioxx: Putting Patient Safety First?*, *supra* at note 23.

¹⁶⁹ See A. J. Wood, "Playing "Kick the FDA"--Risk-Free to Players but Hazardous to Public Health," *The New England Journal of Medicine* 358, no. 17 (Apr 24, 2008), 1774-1775...on the harmful effects in public perception generated by continual criticism of the FDA without discussion of remedies such as additional funding or support.

¹⁷⁰ Zelenay, *The Prescription Drug User Fee Act: Is a Faster Food and Drug Administration always a Better Food and Drug Administration?*, 331, *supra* at note 138, for discussion on the impact of user fees including the harm in spreading the "capture" phenomenon to other FDA divisions. User fees are only available as NDAs are reviewed; any reduction in review rates threatens reviewers' salaries, which are paid primarily by the fees. See also Congressional Research Service and Susan Thaul, *Drug Safety and Effectiveness: Issues and Action Options After FDA Approval* (Washington, DC: U.S. Government Printing Office, 2005), 3, noting that user fees account for more than half of the appropriations to some drug review divisions and up to 80% in others.

¹⁷¹ Food and Drug Administration, *FDA Science and Mission at Risk: Report of the Subcommittee on Science and Technology* (Rockville, MD: FDA, 2007), B-7.

its procedures related to postmarket safety concerns. The IOM had a number of important findings, but faulted the user-fee program in particular for being "excessively oriented toward supporting speed of approval and insufficiently attentive to safety."¹⁷²

Many of the IOM's recommendations to improve drug safety were later incorporated into the Food and Drug Administration Amendments Act of 2007. The statute greatly increased the FDA's authority in the postmarket by granting it 1) the right to mandate and enforce postmarket study requirements in the light of emerging information; 2) the right to limit distribution of drugs using a variety of techniques; 3) the right to force labeling changes; and 4) the right to demand enrollment in a patient registry.¹⁷³ The new statute gave explicit authority for performance linked access programs (sometimes called "safe use" programs) – programs that mandate risk management plans for products with a high potential for misuse - despite the fact that some have criticized these measures as an intrusion into the practice of medicine.¹⁷⁴ Congress also required the FDA, in conjunction with multiple stakeholders, to establish a postmarket risk identification and analysis system.¹⁷⁵

Concurrent with its report to the FDA, the IOM formed the Roundtable on Evidence-Based Medicine to "transform the way evidence on clinical effectiveness is generated and used to improve health and health care."¹⁷⁶ In calling for a "learning healthcare system," the Roundtable recognized that insistence on randomized clinical trials *as the sole mechanism* for developing actionable postmarket evidence *is impractical and inappropriate* given the time, cost, and scope limitations of such methods. These admissions have renewed efforts to improve both the collection of data and the research methodologies employed in pharmacoepidemiology research. Particularly, the IOM calls for "developing the point of care as the knowledge engine," acknowledging that data

¹⁷² Institute of Medicine (IOM), *The Future of Drug Safety: Promoting and Protecting the Health of the Public*, 6, *supra* at note 15.

¹⁷³ Title IX: Enhanced Authorities regarding Postmarket Safety of Drugs in *Food and Drug Administration Amendments Act of 2007*, *Public Law 110-85*, codified in various sections of 21 U.S.C. § 331, 334, 352, 353, 355, 360, 381.

¹⁷⁴ S. Gottlieb, "Drug Safety Proposals and the Intrusion of Federal Regulation into Patient Freedom and Medical Practice," *Health Affairs* 26, no. 3 (May-Jun, 2007), 664-677.

¹⁷⁵ Sec. 905: Active Postmarket Risk Identification and Analysis in *Food and Drug Administration Amendments Act of 2007*, *Public Law 110-85*, codified at 21 U.S.C. § 355(k)(3).

¹⁷⁶ Institute of Medicine (IOM), *Learning Healthcare System Concepts v2008: Annual Report*, *supra* at note 57.

collected in routine clinical care are under-utilized, but ripe to improve patient care.¹⁷⁷ Others have echoed this view.¹⁷⁸ In general, these recognitions underscore the need to develop policies that overcome the evidence generation problems of earlier times. Consensus is needed on the data sets that are necessary both to analyze real-world utilization of products and to create actionable decision points for ongoing benefit-risk analysis.

¹⁷⁷ *ibid.*, 14-15.

¹⁷⁸ M. McClellan, "Drug Safety Reform at the FDA--Pendulum Swing Or Systematic Improvement?" *The New England Journal of Medicine* 356, no. 17 (Apr 26, 2007), 1700-1702; U.S. Department of Health and Human Services, Food and Drug Administration, *The Sentinel Initiative: A National Strategy for Monitoring Medical Product Safety*, 24, *supra* at note 26.

III. Inadequate or Failed Solutions to Develop Postmarket Evidence

Generally, society has underfunded rigorous pharmacoepidemiology efforts to develop postmarket evidence on the performance of prescription medical products. While many entities (e.g., individual physicians, pharmacy and therapeutic committees of health plans) may informally collect anecdotal or observational data on patient experiences, formal postmarket studies – either epidemiologic data analyses or clinical trials – occur at a suboptimal level.¹⁷⁹ This type of information is widely regarded as a classic example of a "public good" in the economics tradition; that is, many stakeholders may capture the benefits of the good or service without underwriting its costs. For this reason, along with the considerable risk associated with postmarket evidence development, it is unlikely that private actors (e.g., pharmaceutical/biotechnology companies or insurance companies) would invest adequately in such efforts.¹⁸⁰ In some cases, additional postmarket studies have revealed the sponsor's product to be inferior to a competing product¹⁸¹, or have revealed new risks that are not offset by benefits.¹⁸² While early warnings on sub-performing products may have the benefits of redirecting R&D efforts and avoiding unpredictable litigation costs, the lack of postmarket studies indicates that private actors generally are not motivated by such benefits.¹⁸³

¹⁷⁹ U.S. Congressional Budget Office, *Research on the Comparative Effectiveness of Medical Treatments: Issues and Options for an Expanded Federal Role*, 8, *supra* at note 6; U.S. Congressional Budget Office, *Research and Development in the Pharmaceutical Industry* (Washington, D.C.: Congress of the U.S., Congressional Budget Office, 2006), 1, <http://purl.access.gpo.gov/GPO/LPS75169>.

¹⁸⁰ U.S. Congressional Budget Office, *Research on the Comparative Effectiveness of Medical Treatments: Issues and Options for an Expanded Federal Role*, 2, 8, *supra* at note 6; Reinhardt, *An Information Infrastructure for the Pharmaceutical Market*, 107-112, *supra* at note 27; Rebecca S. Eisenberg, "An American Dilemma: The Problem of New Uses," *Yale Journal of Health Policy, Law and Ethics* 5 (Summer 2005), 717-718.

¹⁸¹ See, for example, C. P. Cannon and others, "Intensive Versus Moderate Lipid Lowering with Statins After Acute Coronary Syndromes," *The New England Journal of Medicine* 350, no. 15 (Apr 8, 2004), 1495-1504; and accompanying editorial E. J. Topol, "Intensive Statin Therapy--a Sea Change in Cardiovascular Prevention," *The New England Journal of Medicine* 350, no. 15 (Apr 8, 2004), 1562-1564. Bristol Meyers Squibb sponsored a study to show that its Pravachol™ (pravastatin) was to not inferior to Pfizer's Lipitor™ (atorvastatin) and the results of the trial indicated that Lipitor™ (atorvastatin) was superior in lowering the risk of major cardiovascular outcomes.

¹⁸² See discussion in R. S. Bresalier and others, "Cardiovascular Events Associated with Rofecoxib in a Colorectal Adenoma Chemoprevention Trial," *The New England Journal of Medicine* 352, no. 11 (Mar 17, 2005), 1092-1102, on Merck's supplemental clinical trials for new indications on Vioxx™ (rofecoxib) that revealed additional cardiovascular risks.

¹⁸³ Daniel R. Cahoy, "Medical Product Information Incentives and the Transparency Paradox," *Indiana*

Further, because physicians may prescribe drugs off-label, private firms are not compelled to develop supplemental performance information to garner additional markets.¹⁸⁴ Still, a narrow therapeutic indication (i.e., reason for prescribing) will subsequently limit potential physician promotion activities and DTCA, which may significantly blunt market share.¹⁸⁵ Yet, the prevalence of off-label prescribing suggests that physicians do not exert a strong demand for the development of scientific evidence of safety and effectiveness as a pre-requisite to prescribing.¹⁸⁶ While perhaps unintentional, provider behaviors contribute to the lack of a market for postmarket evidence development.¹⁸⁷

Absent adequate private investment, the government has developed postmarket information either using public funding¹⁸⁸, or has relied on a system of 1) economic "carrots," 2) regulatory "sticks," and 3) other indirect private efforts (e.g, interest group activity and litigation) to develop such information. These historical policy solutions are described herein.

Law Journal 82 (Summer 2007), 638... "Costs are reduced when such information is discovered early, before a greater number of people can be affected or the individual harm increases. A rational firm would be expected to invest in uncovering and releasing potentially damaging information in order to minimize these costs."

¹⁸⁴ This circumstance may not always be the case. Merck engaged in a study of Vioxx™ (rofecoxib) partially in response to a similar trial underway for Pfizer's Celebrex™ (celecoxib). Both companies were targeting a prophylactic condition and an FDA-approved indication would permit more aggressive marketing. See Eisenberg, *The Role of the FDA in Innovation Policy*, 377-378, *supra* at note 64.

¹⁸⁵ See U.S. General Accounting Office, *FDA Oversight of Direct-to-Consumer Advertising has Limitations*, GAO-03-177 (Washington, D.C.: GPO, 2002), <http://purl.access.gpo.gov/GPO/LPS31482>.

¹⁸⁶ Sandra H. Johnson, "Polluting Medical Judgment? False Assumptions in the Pursuit of False Claims regarding Off-Label Prescribing," *Minnesota Journal of Law, Science & Technology* 9 (Winter 2008), 72-73; and D. C. Radley, S. N. Finkelstein and R. S. Stafford, "Off-Label Prescribing among Office-Based Physicians," *Archives of Internal Medicine* 166, no. 9 (May 8, 2006), 1021-1026... "Using data from a nationally representative survey of office-based physicians, we found that about 21% of all estimated uses for commonly prescribed medications were off-label, and that 15% of all estimated uses lacked scientific evidence of therapeutic efficacy."

¹⁸⁷ Johnson, *Polluting Medical Judgment? False Assumptions in the Pursuit of False Claims regarding Off-Label Prescribing*, 73, *supra* at note 186.

¹⁸⁸ For example, see J. E. Rossouw and others, "Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women: Principal Results from the Women's Health Initiative Randomized Controlled Trial," *Journal of the American Medical Association* 288, no. 3 (Jul 17, 2002), 321-333; ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, "Major Outcomes in High-Risk Hypertensive Patients Randomized to Angiotensin-Converting Enzyme Inhibitor Or Calcium Channel Blocker Vs Diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)," *Journal of the American Medical Association* 288, no. 23 (Dec 18, 2002), 2981-2997; J. A. Lieberman and others, "Effectiveness of Antipsychotic Drugs in Patients with Chronic Schizophrenia," *The New England Journal of Medicine* 353, no. 12 (Sep 22, 2005), 1209-1223.

A. *The Failed Use of Public "Carrots" to Drive Private Behavior*

1. Limited Market Incentives for the Conduct of Postmarket Studies

Premarket and postmarket data collection by sponsors is largely driven by the FDA's regulatory requirements in conjunction with a company's business plan and tolerance for risk in research and development. Market-based incentive policies for sponsors have emphasized extending the sponsor's period of monopoly in which to sell a product; this "carrot" is granted as a reward for sponsor behavior that contributes to the government's public policy goals.¹⁸⁹ Beginning in 1983 with the Orphan Drug Act, Congress created agency-granted exclusivity, which is an administrative tool that preserves a sponsor's market exclusivity beyond patent expiration.¹⁹⁰ Thus, exclusivity provisions serve as a form of quasi-patent protection by blocking competitor or generic drug entry, and thereby enabling the sponsor to prolong the time period during which monopoly prices can be charged.¹⁹¹ Two types of exclusivity – seven years for orphan drug products¹⁹² and five years for new molecular entities¹⁹³ – are more premarket in orientation and were specifically designed to elicit new drug innovation in therapeutic areas perceived to be underserved or high-risk. Two types of exclusivity deal partially with the postmarket environment: a three-year exclusivity for the completion of new clinical trials for supplemental uses of a previously-approved product (e.g., extending the range of cancers that an oncology drug is approved to treat)¹⁹⁴ and a six-month pediatric exclusivity for performing studies related to children.¹⁹⁵ The former is entirely a

¹⁸⁹ Elizabeth H. Dickinson, "FDA's Role in Making Exclusivity Determinations," *Food and Drug Law Journal* 54 (1999), 195-203.

¹⁹⁰ *Orphan Drug Act*, Public Law 97-414, *Statutes at Large* 96 (January 4, 1983), 2049-2066.

¹⁹¹ Note: Exclusivity *does not* increase the length of a patent. Generally, it is an administrative tool that serves the FDA's public policy goals, and specific statutory mandates dictate its use. For example, orphan drug exclusivity is unique because it blocks both competitor and generic drug entry while most exclusivities simply block generics. See Karena J. Cooper, "Pediatric Marketing Exclusivity--as Altered by the Best Pharmaceuticals for Children Act of 2002," *Food and Drug Law Journal* 57 (2002), 519-544; Eisenberg, *An American Dilemma: The Problem of New Uses*, 717-739, *supra* at note 180.

¹⁹² Sec 527(a): Protection for Unpatented Drugs for Rare Diseases or Conditions in *Orphan Drug Act*, Public Law 97-414, codified at 21 U.S.C. § 360cc.

¹⁹³ *Drug Price Competition and Patent Term Restoration Act of 1984*, Public Law 98-417, *Statutes at Large* 98 (September 24, 1984), 1585-1605., provision codified at 21 U.S.C. § 355(c)(3)(E)(ii).

¹⁹⁴ *ibid.*, provision codified at 21 U.S.C. § 355(c)(3)(E)(iii).

¹⁹⁵ Sec. 111: Pediatric Studies of Drugs in *Food and Drug Administration Modernization Act of 1997*, Public Law 105-115, 2296-2380. Provisions of this Act were subsequently renewed in five years cycles in *Best Pharmaceuticals for Children Act*, Public Law 107-109, *Statutes at Large* 115 (January 4, 2002),

postmarket phenomenon whereas the latter may cover either period, but was initiated in response to marketed drugs.

The three-year supplemental use exclusivity provision was designed to encourage incremental innovation on FDA-approved products. Ideally, clinical tests of new and innovative uses of existing products are driven by data mined from real-world utilization suggesting additional benefits worth studying. While off-label prescribing already permits new uses for existing products, clinical trial on these new uses contributes to a formal evidence base. Thus, it is important to note that the public policy goal is not new use *per se*, but expanded evidence. Specifically, Congress allowed the FDA to grant exclusivity to sponsors that required new clinical trials in order to submit applications that supported new indications (e.g., additional cancers), new dosage formulations (e.g., conversion to a syrup for children), or a shift from prescription to over-the-counter status.¹⁹⁶

This three-year exclusivity is a form of data exclusivity; that is, it blocks a generic drug manufacturer from relying on the innovator sponsor's data to gain FDA approval, which is the typical pathway for generic entry.¹⁹⁷ However, the three-year exclusivity policy has flaws that fail to promote *timely* data creation. First, the grant of exclusivity begins on the date of the approval of the supplemental new drug application (sNDA) and runs concurrently with any other exclusivities, creating an incentive for manufacturers to prolong supplemental clinical trials until close to the expiration of patent life.¹⁹⁸ In this circumstance, the provision fails to spur data creation in response to an unfilled need in a timely manner. Additionally, the data protection *only* applies to the data developed for the supplemental indication; that is, a generic manufacturer can still rely on the data from the original application to enter the market and the generic product may be prescribed off-label for the innovator's planned supplemental indication.¹⁹⁹ Thus, generic entry is not delayed in a *meaningful* way, effectively nullifying any value to sponsors and removing

1408-1424; and Title V: Best Pharmaceuticals for Children Act of 2007 in *Food and Drug Administration Amendments Act of 2007, Public Law 110-85, 823-978*, codified at 21 U.S.C. § 355a(b).

¹⁹⁶ Dickinson, *FDA's Role in Making Exclusivity Determinations*, 201, *supra* at note 189.

¹⁹⁷ Eisenberg, *An American Dilemma: The Problem of New Uses*, 728-729, *supra* at note 180.

¹⁹⁸ *ibid.*, 728.

¹⁹⁹ *ibid.*, 729.

their incentive to perform the studies.²⁰⁰ Indeed, given these circumstances, a sponsor's primary motivation for applying for this exclusivity would be to expand its physician promotion and DTCA activities, which seems a perversion of the original intent.

In 1997, Congress created the pediatric exclusivity provision, which extended monopoly protection by six months if sponsors agreed to fulfill the FDA's requests to conduct studies on the performance of the prescription medical products in children.²⁰¹ Most premarket clinical trials are conducted with adult populations, and thus, healthcare providers must prescribe off-label for children without an evidence base on which to make judgments.²⁰² Prior to this provision, only fifteen percent of pediatric postmarket study commitments were met.²⁰³ Early assessments indicated the program was a success, and it was reauthorized twice in subsequent legislation.²⁰⁴ Sponsors agreed to conduct studies 81% of the time in response to written requests issued by FDA.²⁰⁵ Additionally, both reauthorizations required the FDA to pursue focused reviews of all adverse events for a one-year period following the grant of pediatric exclusivity, adding to the database of postmarket performance in children.²⁰⁶ A focused review requires summary referrals to the Pediatric Advisory Committee and more resource intensity than routine daily

²⁰⁰ Dickinson, *FDA's Role in Making Exclusivity Determinations*, 201, *supra* at note 189; Eisenberg, *An American Dilemma: The Problem of New Uses*, 730, *supra* at note 180.

²⁰¹ Sec. 111: Pediatric Studies of Drugs in *Food and Drug Administration Modernization Act of 1997*, Public Law 105-115 and Dickinson, *FDA's Role in Making Exclusivity Determinations*, 203, *supra* at note 189. Note that the FDA must submit a request for the study in order to qualify.

²⁰² Cooper, *Pediatric Marketing Exclusivity--as Altered by the Best Pharmaceuticals for Children Act of 2002*, 520, *supra* at note 191; R. Roberts and others, "Pediatric Drug Labeling: Improving the Safety and Efficacy of Pediatric Therapies," *Journal of the American Medical Association* 290, no. 7 (Aug 20, 2003), 905-911.

²⁰³ R. Steinbrook, "Testing Medications in Children," *The New England Journal of Medicine* 347, no. 18 (Oct 31, 2002), 1462-1470.

²⁰⁴ See U.S. Department of Health and Human Services, Food and Drug Administration, *The Pediatric Exclusivity Provision: Status Report to Congress* (Rockville, MD: FDA, 2001), 12, <http://www.fda.gov/cder/pediatric/reportcong01.pdf> (accessed January 4, 2009)... "the pediatric exclusivity provision has done more to generate clinical studies and useful prescribing information for the pediatric population than any other regulatory or legislative process to date." See also Roberts and others, *Pediatric Drug Labeling: Improving the Safety and Efficacy of Pediatric Therapies*, 906, *supra* at note 202, "Between July 1998 and April 2002, 53 drugs were granted pediatric exclusivity and 33 drug products have new labels with pediatric information."

²⁰⁵ U.S. Government Accountability Office, *Pediatric Drug Research*, GAO-07-557 (Washington, DC: GPO, 2007), 4, <http://purl.access.gpo.gov/GPO/LPS80423>.

²⁰⁶ P. B. Smith and others, "Safety Monitoring of Drugs Receiving Pediatric Marketing Exclusivity," *Pediatrics* 122, no. 3 (Sep, 2008), e628-33; L. L. Mathis and S. Iyasu, "Safety Monitoring of Drugs Granted Exclusivity Under the Best Pharmaceuticals for Children Act: What the FDA has Learned," *Clinical Pharmacology and Therapeutics* 82, no. 2 (Aug, 2007), 133-134.

monitoring of adverse event reports.²⁰⁷

However, two important qualifications weaken the value of the program, and are worth noting. First, until the passage of the FDAAA in 2007, the FDA lacked an ability to enforce the timely implementation of new labeling information that resulted from the studies, if it was deemed necessary.²⁰⁸ Specifically, the GAO testified, "FDA officials said they have had substantial difficulty in getting drug manufacturers to incorporate unfavorable pediatric research results into drug labels."²⁰⁹ Such a concession to sponsors – granting the exclusivity without mandating the label change – fails to ensure that the postmarket evidence that has been developed is adequately and appropriately used. Now, the FDAAA permits the FDA to refer disputes over label changes to an advisory committee if negotiation with the sponsor fails or is unnecessarily long.²¹⁰ The FDA may also bring enforcement actions against the sponsor.

Second, critics have also contended that the cost to the public of the added exclusivity and delayed generic entry are too large to justify the program's continuation.²¹¹ Upon investigation of these claims, the GAO found that the majority of written requests were issued to sponsors of drugs that return less than \$120 million in sales.²¹² Subsequent economic analyses have focused on the cost effectiveness of the information creation incentive from the perspective of sponsors, finding a high rate of return for blockbusters (i.e., products that return more than \$1 billion in sales), but break-even for other products.²¹³ Therefore, the data remain inconclusive with respect to net social cost, and are most likely highly dependent on the overall market for the drug.

²⁰⁷ *ibid.*

²⁰⁸ Cooper, *Pediatric Marketing Exclusivity--as Altered by the Best Pharmaceuticals for Children Act of 2002*, 537, *supra* at note 191. See also U.S. Government Accountability Office, *Pediatric Drug Research*, 4-5, *supra* at note 205...noting that 40% of the drugs granted pediatric exclusivity that required labeling changes took more than 7 months to implement.

²⁰⁹ U.S. General Accounting Office, *Pediatric Drug Research*, GAO-01-705-T (Washington, D.C.: GPO, 2001), 9, <http://purl.access.gpo.gov/GPO/LPS12893>.

²¹⁰ Sec. 402: Reauthorization of Pediatric Research Equity Act in *Food and Drug Administration Amendments Act of 2007, Public Law 110-85*.

²¹¹ Cooper, *Pediatric Marketing Exclusivity--as Altered by the Best Pharmaceuticals for Children Act of 2002*, 540-541, *supra* at note 191.

²¹² U.S. General Accounting Office, *Pediatric Drug Research*, 6, *supra* at note 209.

²¹³ J. S. Li and others, "Economic Return of Clinical Trials Performed Under the Pediatric Exclusivity Program," *Journal of the American Medical Association* 297, no. 5 (Feb 7, 2007), 480-488... "We focused on the economic incentives to industry of completing pediatric exclusivity and did not account for the economic costs to healthcare incurred by the delay in generic versions of these products appearing on the US market."

On the whole, these exclusivity provisions have been inadequately *implemented* to generate desired results: development, evaluation, management, and communication of postmarket evidence designed to refine the use of marketed products. However, the concept is not the problem. One academic has suggested that exclusivity provisions should be used to generate comparative effectiveness studies and long-term safety studies of marketed pharmaceuticals.²¹⁴ These incentives might promote completion of existing unmet postmarket commitments, many of which focus on conversion of surrogate endpoints (e.g., tumor shrinkage, change in cholesterol levels) into primary endpoints (e.g., morbidity and mortality). Each of these types of studies represents unfulfilled public policy needs and thus is in accordance with Congress's historical rationale.

2. Failed Market Incentives Targeted to Providers

When hospitals and providers are not called upon to conduct formal studies of postmarket evidence, their intuition and expertise are at the heart of the initial identification and assessment of adverse drug experiences (ADEs). ADEs may be the first sign of unexpected risks, but are difficult to discern because of potential co-morbidities and multiple prescriptions. Physicians were among the first to recognize safety issues with antibiotics such as penicillin²¹⁵ and chloramphenicol²¹⁶ in the 1940s and 1950s. From these experiences, the government understood that provider participation was important for further postmarket evidence development. Thus, one of the first attempts to develop postmarket data was to pay physicians and hospitals to report on their patients' experiences with prescription medical products.²¹⁷ This technique, known as spontaneous reporting, occurs when the government (i.e., the FDA) receives a voluntary, isolated

²¹⁴ A. J. Wood, "A Proposal for Radical Changes in the Drug-Approval Process," *The New England Journal of Medicine* 355, no. 6 (Aug 10, 2006), 618-623.

²¹⁵ John J. Powers Jr., "Some Aspects of Certification of Antibiotics Under the Federal Food, Drug, and Cosmetic Act," *Food Drug Cosmetic Law Quarterly* 4 (1949), 340.

²¹⁶ See "Blood Dyscrasia Following the Use of Chloramphenicol," *Journal of the American Medical Association* 149, no. 9 (Jun 28, 1952), 840, in U.S. Senate Committee on the Judiciary and Subcommittee on Antitrust and Monopoly, *Administered Prices in the Drug Industry (Antibiotics -- Appendix B), Part 26*, 15839-15840, *supra* at note 110; Testimony of Albe Watkins U.S. Senate Select Committee on Small Business and Subcommittee on Antitrust and Monopoly, *Competitive Problems in the Drug Industry, Part 6*, 2583-2596, *supra* at note 111.

²¹⁷ U.S. General Accounting Office, *Assessment of the Food and Drug Administration's Handling of Reports on Adverse Reactions from the Use of Drugs*, 20-21, *supra* at note 19; Drug Research Board, National Research Council, *Report of the International Conference on Adverse Reaction Reporting Systems*, 14-15, *supra* at note 19.

report of an ADE. From 1960-1971, the FDA contracted with private and federal hospitals to report ADEs.

The FDA and others developed experience with the system during that decade; its limitations were clear in the early 1970s and have not changed substantially since then.²¹⁸ First, spontaneous reports are noted to be of variable quality and subject to significant underreporting because of the voluntary and discretionary nature of the system.²¹⁹ Consequently, severe sampling biases often occur, making the system ineffective in calculating either incidence or prevalence of a reaction in specific populations.²²⁰ Eventually, the FDA cancelled the payment portion of the program because "it was believed it to be ineffective and so that a more comprehensive and systematic adverse reaction reporting system could be developed."²²¹ Spontaneous reporting notably decreased coincident with the FDA's decision to end contracts.²²² Later studies indicated that physicians did not report because they did not know how or did not have time, they were not encouraged by their employers to report, they did not receive feedback from the FDA, and they feared reporting could be used against them for possible medical malpractice litigation.²²³ The FDA never acted on their intention to create a more comprehensive and systematic infrastructure.

²¹⁸ See generally *ibid.*, *supra* at note 19; U.S. General Accounting Office, *Assessment of the Food and Drug Administration's Handling of Reports on Adverse Reactions from the Use of Drugs*, *supra* at note 19. For more recent summaries of the same criticisms, see also Moore, Psaty and Furberg, *Time to Act on Drug Safety*, 1571-1573, *supra* at note 52; T. Brewer and G. A. Colditz, "Postmarketing Surveillance and Adverse Drug Reactions: Current Perspectives and Future Needs," *Journal of the American Medical Association* 281, no. 9 (Mar 3, 1999), 824-829; S. R. Ahmad, "Adverse Drug Event Monitoring at the Food and Drug Administration," *Journal of General Internal Medicine* 18, no. 1 (Jan, 2003), 57-60; Fontanarosa, Rennie and DeAngelis, *Postmarketing Surveillance--Lack of Vigilance, Lack of Trust*, 2647-2650, *supra* at note 52.

²¹⁹ Drug Research Board, National Research Council, *Report of the International Conference on Adverse Reaction Reporting Systems*, 13-14, 24, *supra* at note 19, "FDA pointed out that, under spontaneous reporting, doctors are reluctant to take the time to report relatively minor, expected, and known reactions which make up the majority of identifiable reactions. FDA said doctors tend to regard drugs as helpful and not to consider that an adverse reaction may be due to a drug they prescribed."

²²⁰ *ibid.*, 14.

²²¹ U.S. General Accounting Office, *Assessment of the Food and Drug Administration's Handling of Reports on Adverse Reactions from the Use of Drugs*, 24, *supra* at note 19.

²²² *ibid.*, 24.

²²³ *ibid.*, 20-21; Drug Research Board, National Research Council, *Report of the International Conference on Adverse Reaction Reporting Systems*, 23-24, *supra* at note 19.

Today, the bulk of the FDA's postmarket efforts still revolve around a spontaneous reporting system.²²⁴ Best estimates gauge only 1-10% of ADEs are captured by the spontaneous reporting system.²²⁵ Despite its poor reputation, the barely noticed strength of the system is its ability to detect rare reactions - on the order of one in one million - at relatively low cost.²²⁶ Brewer and Colditz report on older studies that found "more serious adverse drug reactions have been noted first in case reports than any other method."²²⁷ Some critics of the current system have suggested that more effective reporting would occur if physicians were instructed to report occurrences of particular diseases rather than asking them to make an inference on the potential association between an ADE and an antecedent drug.²²⁸

To remedy the lack of incidence and prevalence data on ADEs, the FDA tried another market incentive program in the late 1960s. For a brief period, the FDA experimented with contracts for a companion monitoring program known as intensive surveillance, the precursor to a concept today known as "active surveillance."²²⁹ Intensive surveillance was performed by monitoring the entire medical care record on a randomly selected number of inpatient hospital beds.²³⁰ It had the aim of "providing reasonably adequate quantification of relations between drug use and adverse events in a well-

²²⁴ Institute of Medicine (IOM), *The Future of Drug Safety: Promoting and Protecting the Health of the Public*, 53-55, *supra* at note 15; Moore, Psaty and Furberg, *Time to Act on Drug Safety*, 1571-1573, *supra* at note 52.

²²⁵ U.S. General Accounting Office, *Adverse Events: The Magnitude of Health Risk is Uncertain Because of Limited Incidence Data*, 10, citing Goldman and others, *The Clinical Impact of Adverse Event Reporting*, *supra* at note 18.

²²⁶ Drug Research Board, National Research Council, *Report of the International Conference on Adverse Reaction Reporting Systems*, 6, 12-13, *supra* at note 19.

²²⁷ Brewer and Colditz, *Postmarketing Surveillance and Adverse Drug Reactions: Current Perspectives and Future Needs*, 825, *supra* at note 218. See also E. M. Rodriguez, J. A. Staffa and D. J. Graham, "The Role of Databases in Drug Postmarketing Surveillance," *Pharmacoepidemiology and Drug Safety* 10, no. 5 (Aug-Sep, 2001), 407-410.

²²⁸ Reidenberg, *Improving How we Evaluate the Toxicity of Approved Drugs*, 2, *supra* at note 52... "Physicians can report cases to diagnosis registries very well...A physician's training is to make diagnoses but be wary of making associations based on timing only. The wariness is important because if something precedes an event, one cannot assume that it caused the event. Doctors learn that properly controlled investigations are needed to determine causality."

²²⁹ U.S. Department of Health Education and Welfare and Review Panel on New Drug Regulation, *Interim Report: Staff Paper: Adverse Drug Reaction Reporting Systems* (Washington, DC: DHEW, 1977), 11.

²³⁰ U.S. Food and Drug Administration, Wallace F. Janssen and Alexander M. Schmidt, *Annual Reports 1950-1974 on the Administration of the Federal Food, Drug, and Cosmetic Act and Related Laws* (Rockville, MD: Dept. of Health, Education, and Welfare; Public Health Service; Food and Drug Administration; U.S. Government Printing Office, 1977), 958.

defined group of treated patients."²³¹ It was lauded for the ability to determine incidence of known adverse events, to detect previously unsuspected adverse reactions, to identify drug interactions, and to determine patterns of drug use and misuse.²³² However, in 1972, it was discontinued due to fiscal mismanagement and an ineffective yield of information on ADEs despite the high cost of the program.²³³ A few monitoring contracts remained throughout the 1970s and 1980s at the Boston Collaborative Drug Surveillance Program, and today four "task orders" (i.e., contracts) form the backbone of external pharmacoepidemiology research that still exists at the FDA.²³⁴ The FDA is reviving the spirit of the intensive surveillance program via Congress's mandate to create an active postmarket risk identification and analysis system.²³⁵ Whether the program will be structured with market-based incentives for providers is still uncertain, but the legislation requires collaboration with private sources and the use of private sector electronic health data.

3. Impotent Use of Reimbursement Policies Designed to Develop Evidence

Payors (i.e., health plans) have a more natural role in demanding scientific evidence of safety and effectiveness of marketed prescription medical products as the purchasers of these goods and services, particularly in an era of rapidly increasing healthcare costs. Reimbursement decisions can act as significant incentives or disincentives to manufacturers, and consequently, can drive development of evidence in the premarket or postmarket phase. However, for most prescription medical products, there is not significant leeway; that is, the largest payor - the CMS - is required by law to cover, or pay for, all FDA-approved uses and any off-label uses that have been captured in

²³¹ Drug Research Board, National Research Council, *Report of the International Conference on Adverse Reaction Reporting Systems*, 8, *supra* at note 19.

²³² *ibid.*, 8.

²³³ U.S. General Accounting Office, *Assessment of the Food and Drug Administration's Handling of Reports on Adverse Reactions from the Use of Drugs*, 3, 26, *supra* at note 19... Approximately 2% of total ADE reports were generated using the intensive monitoring method.

²³⁴ U.S. Office of Technology Assessment, *Postmarketing Surveillance of Prescription Drugs*, 42, *supra* at note 19; Institute of Medicine (IOM), *The Future of Drug Safety: Promoting and Protecting the Health of the Public*, 111-112, *supra* at note 15.

²³⁵ Sec. 905: Active Postmarket Risk Identification and Analysis in *Food and Drug Administration Amendments Act of 2007, Public Law 110-85*, codified at 21 U.S.C. § 355(k)(3).

approved compendia.²³⁶ To wit, the Congressional Budget Office has suggested, "the limited demand for such research from such a prominent payer [CMS] has constrained the supply correspondingly."²³⁷

Thus, in 2005, it was a significant surprise when the CMS announced that it would *only* agree to cover off-label uses of four prescription biologics to treat colorectal cancer *in approved clinical trials*.²³⁸ This type of coverage became known as coverage with evidence development (CED), a "third" and controversial pathway for reimbursement with questionable legal standing.²³⁹ Recently, the CMS has published guidance on CED, which has been split into two programs: 1) Coverage with Appropriateness Determination which requires that clinicians submit clinical data to a patient registry (i.e., an observational data collection mechanism) along with their claim for reimbursement, and 2) Coverage with Study Participation (CSP) which requires participation in a clinical trial as a pre-condition for reimbursement of a product that would otherwise have insufficient evidence to support a "reasonable and necessary" determination (i.e., the regulatory standard for coverage).²⁴⁰ Setting aside the uncertain legal standing, the CED's main public policy aim was "to facilitate longitudinal data collection that would ultimately assist doctors and patients in better understanding the risks, benefits and costs of alternative diagnostic and treatment options."²⁴¹ However, rules that went into effect in November 2008 expanded the number of compendia used for coverage decisions, essentially eliminating the chance that off-label uses will not be listed.²⁴² Thus, for drugs and biologics, the policy is toothless; its ability to influence devices and diagnostics will become clearer in the coming years.

²³⁶ S. R. Tunis and S. D. Pearson, "Coverage Options for Promising Technologies: Medicare's 'Coverage with Evidence Development'," *Health Affairs* 25, no. 5 (Sep-Oct, 2006), 1218-1230.

²³⁷ U.S. Congressional Budget Office, *Research on the Comparative Effectiveness of Medical Treatments: Issues and Options for an Expanded Federal Role*, 9, *supra* at note 6.

²³⁸ Centers for Medicare and Medicaid Services, "Decision Memo for Anticancer Chemotherapy for Colorectal Cancer (CAG-00179N)," CMS, <http://www.cms.hhs.gov/mcd/viewdecisionmemo.asp?id=90>

²³⁹ See Carnahan, *Medicare's Coverage with Study Participation Policy: Clinical Trials Or Tribulations?*, 229-272, *supra* at note 75, for comments on legal challenges.

²⁴⁰ Centers for Medicare and Medicaid Services, "National Coverage Determinations with Data Collection as a Condition of Coverage: Coverage with Evidence Development," CMS, http://www.cms.hhs.gov/mcd/ncpc_view_document.asp?id=8

²⁴¹ Tunis and Pearson, *Coverage Options for Promising Technologies: Medicare's 'Coverage with Evidence Development'*, 1218-1230, *supra* at note 236.

²⁴² Abelson and Pollack, *Medicare Widens Drugs it Accepts for Cancer Care*, 1, *supra* at note 87.

B. The Failed Use of Regulatory "Sticks" to Drive Behavior

With respect to postmarket evidence generation and management, sticks - in the form of penalties or restrictions to mandate compliance – have evolved often as a policy of last resort after all other efforts to voluntarily achieve desired outcomes have failed. As noted earlier, together the spontaneous reporting system and postmarket clinical trials comprise the bulk of the FDA's data collection, which is intended to stimulate benefit-risk assessment and to inform risk management and risk communication. Lacking relevant enforcement powers for both systems until very recently, the FDA struggled to negotiate any postmarket risk management changes (e.g., labeling changes, "Dear Healthcare Provider" letters, etc) with sponsors and rarely used its only powerful threat, withdrawal of the product. Since the passage and implementation of the FDAAA, the FDA now has a less blunt enforcement option: the power to assess civil monetary penalties against sponsors that fail to perform a variety of postmarket requirements.²⁴³

Additionally, the FDA now has the legal authority to demand such requirements; that is, FDA may require labeling changes, continuing evidence generation through studies or clinical trials, and safe use programs (known as performance linked access systems) based on analyses of emergent postmarket data or unsettled safety and effectiveness questions at the time of marketing.²⁴⁴ These new regulatory powers are still uncertain because rulemaking and guidance have not been published on the FDA's implementation plans.²⁴⁵ A review of the FDA's historical struggles with regulatory rules to generate postmarket data follows.

1. Mismanaged Spontaneous Reporting Requirements

Following the first wave of innovation in pharmaceutical products that took place between 1935 and 1955, the FDA struggled to cope with the new and complex benefit-

²⁴³ Sec. 902: Enforcement in *Food and Drug Administration Amendments Act of 2007, Public Law 110-85*, codified in 21 U.S.C. § 333.

²⁴⁴ Title IX: Enhanced Authorities regarding Postmarket Safety of Drugs in *Food and Drug Administration Amendments Act of 2007, Public Law 110-85*, codified in various sections of 21 U.S.C. § 331, 334, 352, 353, 355, 360, 381.

²⁴⁵ See Kessler and Vladeck, *A Critical Examination of the FDA's Efforts to Preempt Failure-to-Warn Claims*, 490, *supra* at note 61... "The FDA Amendments Act tries to strengthen the agency's ability to conduct post-approval surveillance, but it is far from clear whether these efforts will bear fruit."

risk profiles of available products.²⁴⁶ After failing to obtain adequate evidence via *voluntary* reporting mechanisms, a citizens advisory committee deemed the FDA's spontaneous reporting programs insufficient to protect the consumer.²⁴⁷ The committee stated:

"The interests of the consumer would be better protected if all drug manufacturers and all qualified physicians were required to report to FDA at once any information concerning significant adverse reactions or occurrences of such reactions, and that FDA should have the responsibility for seeing that prompt action is taken to protect the public."²⁴⁸

Yet, the FDA did not have the authority to command reporting and began to lobby for that authority in legislation that would become the 1962 Kefauver-Harris Amendments.²⁴⁹ In presenting its case, the FDA reported that sponsors were aware of case reports of significant injuries and deaths associated with their product's use and these sponsors failed to inform the FDA until years after the damage was done.²⁵⁰ The FDA's eventual knowledge of these events led to the drug's removal from the market. The FDA argued before Congress, "...had full reports of the experience with these drugs been submitted as soon as the manufacturers received them, undoubtedly it would have saved lives."²⁵¹

Since the 1962 Amendments, the vast majority of spontaneous reports originate with sponsors, and late reports and underreporting have not been uncommon.²⁵² Several critics have noted that sponsors have inherent conflicts of interest in reporting on their own products especially when there is leeway in determining whether the drug and

²⁴⁶ Hilts, *Protecting America's Health: The FDA, Business, and One Hundred Years of Regulation*, 105, *supra* at note 65.

²⁴⁷ U.S. Citizens Advisory Committee on the Food and Drug Administration, *Report of Second Citizens Advisory Committee on the Food and Drug Administration to the Secretary of Health, Education, and Welfare*, 1962), reprinted in *Food Drug and Law Journal* 17, no. 10 (October, 1962), 622.

²⁴⁸ *ibid.*

²⁴⁹ Note: the FDA was only interested in mandating reporting from sponsors. It largely ignored the idea of mandatory physician reporting.

²⁵⁰ U.S. Senate Committee on Government Operations, *Interagency Coordination of Information, Part 1*, 87th Cong., 2d sess., 1963, 381-382. The three products, approved for non-life threatening conditions, cited as examples, included suppressed reports of 54 cases of hepatitis and jaundice and at least 22 deaths. One firm had waited five years before submitting case reports to the government.

²⁵¹ *ibid.*, 381-382.

²⁵² See Ahmad, *Adverse Drug Event Monitoring at the Food and Drug Administration*, 57-60, *supra* at note 218... discussing criminal actions against noncompliant sponsors. Most recently, see U.S. Department of Health and Human Services. Food and Drug Administration, "Warning Letter to Jean-Paul Garnier, Chief Executive Officer of GlaxoSmithKline (08-ATL-05)," FDA, http://www.fda.gov/foi/warning_letters/s6714c.htm

outcome are linked.²⁵³ To that end, there have been calls for expert analysis and critical oversight of sponsor-generated reports by other members of the scientific community.²⁵⁴

Regardless of the number and quality of reports received, historically, the FDA medical officers ignored or minimized the data. In 1974, 1982, and 1986, the GAO reported that collected spontaneous reporting information and subsequent assessment had not contributed to postmarket regulatory decisions in risk management.²⁵⁵ Most of the FDA's medical officers were unaware of the program or discounted its usefulness since it could not systematically prove or disprove causal relationships between drugs and outcomes (i.e., it was not the type of data to which they were accustomed and heavily preferred). The FDA employees performing pharmacoepidemiology research and analyses had little to no power to compel action as a result of their findings, and consequently, were left with little recourse when their efforts were under-utilized.²⁵⁶ Also, without an equal share of the resources or organizational prestige and power at FDA²⁵⁷, the pharmacoepidemiology staff had little opportunity or support to develop

²⁵³ See B. M. Psaty and others, "Potential for Conflict of Interest in the Evaluation of Suspected Adverse Drug Reactions: Use of Cerivastatin and Risk of Rhabdomyolysis," *Journal of the American Medical Association* 292, no. 21 (Dec 1, 2004), 2622-2631; B. L. Strom, "Potential for Conflict of Interest in the Evaluation of Suspected Adverse Drug Reactions: A Counterpoint," *Journal of the American Medical Association* 292, no. 21 (Dec 1, 2004), 2643-2646.

²⁵⁴ Drug Research Board, National Research Council, *Report of the International Conference on Adverse Reaction Reporting Systems*, 12, *supra* at note 19.

²⁵⁵ U.S. General Accounting Office, *Assessment of the Food and Drug Administration's Handling of Reports on Adverse Reactions from the Use of Drugs*, 10-15, 34, 39-43, *supra* at note 19; U.S. General Accounting Office, *FDA can further Improve its Adverse Drug Reaction Reporting System: Report to the Secretary of Health and Human Services*, 13-20, *supra* at note 19... The 1982 finding that 44% of reports were not entered into the database was investigated by Congress to determine the FDA's role in keeping Zomax on the market despite fatalities linked to its use. See U.S. House Committee on Government Operations, *FDA's Regulation of Zomax*, 98th Cong., 1st sess., 1983. See also U.S. General Accounting Office, *Drug Regulation: FDA's Computer Systems Need to be Better Managed*, GAO/IMTEC-86-32 (Washington, DC: GPO, 1986), 3, finding 79% of medical officers never used the adverse drug reaction reporting system and 25% of reports had not been entered into the computer system.

²⁵⁶ See U.S. Government Accountability Office, *Improvement Needed in FDA's Postmarket Decision-Making and Oversight Process*, 12-29, *supra* at note 15... "ODS [Office of Drug Safety] serves primarily as a consultant to OND [Office of New Drugs] and does not have independent decision-making responsibility" and Testimony of David J. Graham in U.S. Senate Committee on Finance, *FDA, Merck, and Vioxx: Putting Patient Safety First?*, 13-49, 124-138, 189-203, *supra* at note 23 and U.S. House Committee on Energy and Commerce, *The Adequacy of FDA Efforts to Assure the Safety of the Drug Supply*, 110th Cong., 1st sess., 2007, 56-78.

²⁵⁷ See U.S. Government Accountability Office, *Improvement Needed in FDA's Postmarket Decision-Making and Oversight Process*, 12-29, *supra* at note 15; Zelenay, *The Prescription Drug User Fee Act: Is a Faster Food and Drug Administration always a Better Food and Drug Administration?*, 292-293, 311-313, *supra* at note 138; Avorn, *In Defense of Pharmacoepidemiology--Embracing the Yin and Yang of Drug Research*, 2219-2220, *supra* at note 107... "At the Food and Drug Administration, drug-epidemiology

innovative algorithms for improved risk identification and assessment methods that might have influenced their colleagues.²⁵⁸ In general, regulatory policies to force collection of postmarket data ultimately failed because of technical and organizational mismanagement.

The FDA held a public workshop designed to solicit input for a future research proposal directed at the “research approaches and methods associated with the best ways to assess the public health benefit of collecting and reporting all adverse events.”²⁵⁹ At that workshop, the public’s focus was less on the effectiveness of a stand-alone spontaneous reporting system, but on how it could work in conjunction with the planned active surveillance system (recall this is a mechanism to gather data by mining existing electronic health records and claims data on a systematic basis).²⁶⁰ Thus, general disinterest in spontaneous reporting continues to confound policies designed to use it as a tool for evidence development and evaluation. Its useful incorporation in future public health information infrastructure merits more consideration.

2. Impotent Postmarket Study Commitment Enforcement

The other major data collection activity in the postmarket environment is either epidemiology studies or controlled clinical trials (sometimes known as Phase IV studies) discussed earlier in this chapter. Recall that Phase IV studies were first designed to deal with the risky yet promising breakthrough Parkinson’s drug levodopa, which required

activities have long been relegated to second-class status.”

²⁵⁸ See Institute of Medicine (IOM), *The Future of Drug Safety: Promoting and Protecting the Health of the Public*, 108-110, *supra* at note 15...“Little has been done to optimize the usage of AERS [adverse event reporting system] for drug safety signal detection until recently.”

²⁵⁹ Food and Drug Administration and Department of Health and Human Services, “Maximizing the Public Health Benefit of Adverse Event Collection Throughout a Product’s Marketed Life Cycle; Public Workshop; Request for Comments,” *Federal Register* 72, no. 246 (December 26, 2007), 73029-73030, <http://edocket.access.gpo.gov/2007/pdf/E7-24960.pdf>.

²⁶⁰ Food and Drug Administration and Department of Health and Human Services, “Transcript of a Public Workshop: Maximizing the Public Health Benefit of Adverse Event Collection Throughout the Productive Life Cycle,” FDA, [http://www.fda.gov/ohrms/dockets/dockets/07n0480/FDA-2007-N-0000-TR-\(07N-0480\).pdf](http://www.fda.gov/ohrms/dockets/dockets/07n0480/FDA-2007-N-0000-TR-(07N-0480).pdf)...“there are a number of things that are changing very rapidly that are almost certainly going to be important fixtures in the healthcare landscape that I think would have an important bearing on what we would want from a passive surveillance system. Specifically, it is very likely that there is going to be a much more robust active surveillance system...”

ongoing data collection *after approval* to study its longitudinal effects.²⁶¹ Soon after the levodopa experiment, Phase IV trial commitment language began increasing dramatically in letters to sponsors announcing approvals for their products despite FDA's questionable authority to enforce these commitments routinely.²⁶² It was not until the late 1980s that the FDA formalized its practice of seeking voluntary commitments for postmarket data gathering. Regulations for fast track (Subpart E approvals) stated:

“If FDA approval is gained on the basis of limited, but sufficient, clinical trials, it *will usually be important* to conduct postmarketing (phase IV) clinical studies that will extend the knowledge about the drug’s safety and efficacy and allow physicians to optimize its use.”²⁶³ [emphasis added]

The FDA’s qualified speech with regard to its postmarket powers is indicative of the perceived weakness of its statutory position. Essentially, the completion of the studies under *voluntary* commitments was unenforceable. As of 2006, only 9% of the open commitments were required by law or statute.²⁶⁴

It was not until 1992 when the FDA promulgated accelerated approval (Subpart H) rules for patients with "severely-debilitating" or "immediately" life-threatening illnesses did Phase IV study commitments become mandatory, and thus, enforceable.²⁶⁵ These studies were intended to prove the correlation between the unverified surrogate endpoints used in premarket clinical trials (e.g., tumor shrinkage in oncology trials) and the more traditional clinical endpoint (e.g., survival). The FDA also developed quick withdrawal procedures should the postmarket studies fail to meet traditional clinical endpoints in subsequent study.²⁶⁶

²⁶¹ See Food and Drug Administration and Department of Health, Education, and Welfare, *Approved New Drugs that Require Continuation of Long-Term Studies, Records, and Reports; Listing of Levodopa*, 201-202, *supra* at note 120.

²⁶² Steenburg, *The Food and Drug Administration's Use of Postmarketing (Phase IV) Study Requirements: Exception to the Rule?*, 319, *supra* at note 118; Department of Health and Human Services Office of the Inspector General, *Postmarketing Studies of Prescription Drugs*, OEI-03-94-00760 (Washington, DC: OIG, 1996), 5.

²⁶³ Food and Drug Administration and Department of Health and Human Services, *Investigational New Drug, Antibiotics, and Biological Drug Product Regulations; Procedures for Drugs Intended to Treat Life-Threatening and Severely Debilitating Illnesses*, 41516-41524, *supra* at note 127.

²⁶⁴ Department of Health and Human Services Office of the Inspector General, *FDA's Monitoring of Postmarket Study Commitments*, OEI-01-04-00390 (Washington, DC: OIG, 2006), 8.

²⁶⁵ Food and Drug Administration and Department of Health and Human Services, *New Drug, Antibiotic, and Biological Drug Product Regulations; Accelerated Approval*, 58942-58960, *supra* at note 128.

²⁶⁶ *ibid.*

Despite significant hope for a more responsive system for safety and effectiveness data, Phase IV trials failed because so few postmarket commitments were realized. As of September 30, 2007, only 14% of New Drug Applications (NDAs) and 24% of Biological License Applications (BLAs) have ongoing studies.²⁶⁷ Completion numbers were worse at 12% for NDAs and 20% for BLAs. More than 1000 commitments have not been initiated and hold a status of "pending" indicating that they are not "delayed" and still "planned." Yet, some of the marketing approval dates on the applications with a "pending" status are more than a decade past.²⁶⁸ Critics have noted that the FDA's threat of quick withdrawal for the failure to correlate surrogate endpoints with clinical endpoints has been empty since *no drugs have been removed for a failure to complete a study*.²⁶⁹ In addition to finding general mismanagement and a lack of global understanding of the outstanding commitments, the Inspector General faulted the FDA's drug review divisions for failing to track progress on postmarket studies, and consequently, failing to pursue the status of their completion.²⁷⁰ In short, the FDA's attempts to generate postmarket evidence via Phase IV studies have demonstrated the agency's impotence, and it will be difficult to shift the culture of complacency that has arisen.

3. Underused Risk Management Programs

Recall from the chloramphenicol case in the previous chapter that sometimes the mere generation and dissemination of postmarket evidence is inadequate to assure safe and effective use of prescription medical products. The FDA's information dissemination channels compete for attention with the marketing budgets of large corporations intent on selling their products. The FDA's primary attempt to communicate benefit-risk

²⁶⁷ Food and Drug Administration and Department of Health and Human Services, "Report on the Performance of Drugs and Biologics Firms in Conducting Postmarketing Commitment Studies; Availability," *Federal Register* 73, no. 80 (April 24, 2008), 22157-22159, <http://edocket.access.gpo.gov/2008/pdf/E8-9007.pdf>.

²⁶⁸ See Center for Drug Evaluation and Research, Food and Drug Administration, "Postmarketing Study Commitments," FDA, <http://www.accessdata.fda.gov/scripts/cder/pmc/index.cfm>... Celebrex™ (celecoxib) has a Phase IV commitment dating back to December 23, 1999 for familial adenomatous polyposis and Botox™ (botulinum toxin type A) has a Phase IV pediatric commitment dating back to December 12, 1991 as a few examples.

²⁶⁹ Wood, *A Proposal for Radical Changes in the Drug-Approval Process*, 618-623, *supra* at note 214.

²⁷⁰ Department of Health and Human Services Office of the Inspector General, *FDA's Monitoring of Postmarket Study Commitments*, 17-18, *supra* at note 264.

information to the public and providers is via the labeling on the package. If emergent evidence changes the benefit-risk profile of the product, the FDA must negotiate warnings and other types of information dissemination with the product's sponsor, which may delay the delivery of safe and effective care.²⁷¹ However, regardless of the sponsor's responsiveness to change requests, studies have found that increasing the warning levels in labeling is ineffective at stemming contraindicated (or inappropriate) use.²⁷² Ultimately, some prescription medical products have been removed from the market because sponsors and regulators have not taken adequate action to control improper utilization, which arises from misunderstanding the risks of the product.

In cases when more aggressive risk management is necessary, the FDA's next policy option is to negotiate a restricted distribution program (alternatively known as a performance-linked access system or a safe use program), or failing that, withdraw the product. Certain products have such severe adverse side effects that they prompt the FDA's involvement in risk management and risk communication policies to continue to collect and monitor postmarket evidence to mitigate against misuse. Classic examples include products with teratogenic risks such as thalidomide or Accutane™ (isotretinoin). Legally, the FDA's ability to enforce restricted distribution programs has historically been shaky, and so its usefulness as a regulatory mandate has been limited. FDA's first restricted distribution program did not survive court challenge; both the district court and the appellate court found that the FDA had acted beyond its statutory mandate.²⁷³ Legislation to overturn the court's decision was also opposed by physicians who protested

²⁷¹ See Testimony of Sandra Kweder in U.S. Senate Committee on Finance, *FDA, Merck, and Vioxx: Putting Patient Safety First?*, *supra* at note 23... on the well-publicized case of delayed labeling changes to Vioxx™ (rofecoxib). It took over a year for the FDA to negotiate the addition of a warning on the risks of heart attack and stroke to the label. Since the enactment of the 2007 FDAAA, Congress has narrowed the permissible negotiation time to less than 90 days. See Sec. 901: Postmarket Studies and Clinical Trials regarding Human Drugs; Risk Evaluation and Mitigation Strategies in *Food and Drug Administration Amendments Act of 2007, Public Law 110-85*, codified as 21 U.S.C. § 355(o)(4).

²⁷² Smalley and others, *Contraindicated Use of Cisapride: Impact of Food and Drug Administration Regulatory Action*, 3036-3039, *supra* at note 69; Graham and others, *Liver Enzyme Monitoring in Patients Treated with Troglitazone*, 831-833, *supra* at note 70. For a summary of failures in FDA risk communication, see S. A. Goldman, "Communication of Medical Product Risk: How Effective is Effective Enough?" *Drug Safety* 27, no. 8 (2004), 519-534. Notwithstanding these findings, an FDA epidemiologist has suggested that black box warnings may reduce improper utilization because they serve the additional function of limiting DTCA. See Testimony of David Graham in U.S. Senate Committee on Finance, *FDA, Merck, and Vioxx: Putting Patient Safety First?*, 27, *supra* at note 23.

²⁷³ *American Pharmaceutical Asso. v. Weinberger*, 824, *supra* at note 92; *American Pharmaceutical Asso. v. Mathews*, No. 74-1989, 174 (United States Court of Appeals for the District of Columbia Circuit 1976).

certain provisions, such as limitations on prescribing to certain board-certified specialties, as interference in the practice of medicine.²⁷⁴

Because all drug reform legislation failed in the late 1970s, the court case formally was not overturned. Nonetheless, the FDA persisted in asserting its statutory authority to create such programs for safe and effective use.²⁷⁵ Similar to FDA's dubious ability to enforce postmarket study commitments, enforcement of restricted distribution programs was limited to particular circumstances (Subpart H approvals), which were later affirmed by Congress as statute.²⁷⁶ The uncertain statutory ground perhaps led to limited use of this tool to accomplish the following goals: 1) to actively monitor patients prescribed products with known fatal or teratogenic side effects via enrollment in a registry program;²⁷⁷ 2) to limit prescribing to certain providers or hospitals that have had special training in addition to monitoring;²⁷⁸ and 3) to require assent that physicians and patients have completed training or read specific educational materials.²⁷⁹

Using the threat of withdrawal, the FDA is able to demand such programs, but they are hardly routine.²⁸⁰ Development of postmarket evidence in this way is reserved for prescription medical products that are known to be extraordinarily high-risk. In 2007, Congress gave the FDA firm statutory authority to enact these programs, termed "safe

²⁷⁴ U.S. General Accounting Office, *FDA Drug Approval: A Lengthy Process that Delays the Availability of Important New Drugs*, 51-53, *supra* at note 21, describing the various constituencies that testified against the provision; U.S. Department of Health Education and Welfare and Review Panel on New Drug Regulation, *Interim Report: Expansion of FDA Statutory Authority in the Post-Marketing Period for New Drugs*, 9, *supra* at note 93. See commentary in Kessler, *Regulating the Prescribing of Human Drugs for Nonapproved Uses Under the Food, Drug, and Cosmetic Act*, 693-760, *supra* at note 71; and Shapiro, *Limiting Physician Freedom to Prescribe a Drug for any Purpose: The Need for FDA Regulation*, 801-872, *supra* at note 93.

²⁷⁵ Jeffrey E. Shuren, "The Modern Regulatory Administrative State: A Response to Changing Circumstances," *Harvard Journal on Legislation* 38 (Summer 2001), 310... "The FDA noted that the District of Columbia Court of Appeals recognized that restricted use, such as restrictions to a prescription-only basis, are sometimes necessary to ensure that persons who intend to use the drug consistent with its label can do so."

²⁷⁶ *ibid.*, 312-313, explaining Congress's implicit approval of restricted distribution.

²⁷⁷ For example, see *ibid.*, 310, 313, describing programs for Clozaril™ (clozapine), an antipsychotic known to cause agranulocytosis and thalidomide, an anti-leprosy drug known as a teratogen.

²⁷⁸ For example, see Food and Drug Administration, "FDA Approves Resumed Marketing of Tysabri Under a Special Distribution Program," FDA, <http://www.fda.gov/bbs/topics/NEWS/2006/NEW01380.html> requiring monitoring for rare, fatal conditions associated with Tysabri™ (natalizumab) use.

²⁷⁹ For a complete list of Subpart H restricted distribution programs, see U.S. Government Accountability Office, *Approval and Oversight of the Drug Mifeprex*, GAO-08-751 (Washington, DC: GPO, 2008), 28.

²⁸⁰ Institute of Medicine (IOM), *The Future of Drug Safety: Promoting and Protecting the Health of the Public*, 167-170, *supra* at note 15.

use" in the legislation, but demanded a reasonable showing of evidence to predicate their use.²⁸¹ The irony of this situation is that some products, *which today are marketed exclusively and conditionally on the maintenance a safe use program*, had to be temporarily removed from the market when risks were first identified because no data was routinely collected that would inform stakeholders of the risk.²⁸² One wonders if the affected companies would have been better off had they launched their products with a small monitoring campaign that could later be discontinued as stakeholders established familiarity with a product's benefits and risks. As it stands, these regulatory measures remain underused due to a chicken-and-egg problem: a run-of-the-mill lack of evidence is not a persuasive enough showing to trigger the safe use implementation.

C. *Inconsistent Private Sector Efforts to Develop Postmarket Evidence*

1. Use of Registries through Private Organizations.

Another related form of a performance-linked access system or safe use program is a patient registry, defined as an "organized system that uses observational study methods to collect uniform data to evaluate specified outcomes for a population and that serves a predetermined scientific, clinical, or policy purpose."²⁸³ Historically, these registries were physician-organized networks for collecting detailed patient information, often defined by a particular disease or treatment.²⁸⁴ The American Medical Association formed the Committee on Blood Dyscrasias in 1955, which was the first diagnosis-based registry to systematically track adverse reactions.²⁸⁵ Medical journals often reported on unique cases, but a centralized registry of diagnostic outcomes was never attempted. The registry

²⁸¹ Sec. 901: Postmarket Studies and Clinical Trials regarding Human Drugs; Risk Evaluation and Mitigation Strategies in *Food and Drug Administration Amendments Act of 2007, Public Law 110-85*, codified as 21 U.S.C. § 355-1.

²⁸² For examples, see Institute of Medicine (IOM), *The Future of Drug Safety: Promoting and Protecting the Health of the Public*, 59, *supra* at note 15, for story of Lotronex™ (alosetron); Food and Drug Administration, *FDA Approves Resumed Marketing of Tysabri Under a Special Distribution Program*, *supra* at note 278, for story of Tysabri™ (natalizumab).

²⁸³ R. E. Gilkich and N. A. Dreyer, *Registries for Evaluating Patient Outcomes: A User's Guide*, AHRQ-07-EHC001-1 (Rockville, MD: Agency for Healthcare Research and Quality (AHRQ), 2007), 1.

²⁸⁴ Institute of Medicine (IOM), *Evidence-Based Medicine and the Changing Nature of Health Care: 2007 IOM Annual Meeting Summary*, 132-141, *supra* at note 7.

²⁸⁵ U.S. Department of Health Education and Welfare and Review Panel on New Drug Regulation, *Interim Report: Staff Paper: Adverse Drug Reaction Reporting Systems*, 9-10, *supra* at note 229; Drug Research Board, National Research Council, *Report of the International Conference on Adverse Reaction Reporting Systems*, 11, *supra* at note 19; Reidenberg, *Improving how we Evaluate the Toxicity of Approved Drugs*, 1-2, *supra* at note 52.

was a successful experiment because the blood disorder in question was rare enough that notable increases in frequency were attributable to a limited set of causes.

Following the blood dyscrasias registry, several additional disease registries were formed in addition to outcome registries, which collected data on specific adverse reactions (e.g., outcomes that affected the eye).²⁸⁶ These registries were private and typically organized by interest groups, but the FDA lent financial support to their maintenance and accessed their data as required.²⁸⁷ For example, the Registry of Hepatic Toxicity to Drugs was credited with providing the necessary information to remove ticrynafen, a diuretic intended to treat hypertension, from the market six months after it was introduced due to liver toxicities.²⁸⁸ In 2004, eight registries existed to track specific drug-outcome reactions in addition to 14 medication-based/product registries.²⁸⁹ There are also many device-based registries operated by public and private sources that monitor long-term implantable device performance.²⁹⁰

Interest in registries has grown in recent years.²⁹¹ The AHRQ's development of registry standards²⁹² and the CMS's CED policy have reinforced this popularity.²⁹³ One large healthcare insurer has attempted to incent provider involvement in registries by awarding "Premium Provider Status" to participating providers.²⁹⁴ Still, registries are voluntary and the supporting funding – not only to manage and generate the data, but to supervise patient privacy concerns, informed consent, and patient recruitment - is substantial.²⁹⁵ The American Medical Association Adverse Reaction Registry and a

²⁸⁶ U.S. General Accounting Office, *FDA Drug Approval: A Lengthy Process that Delays the Availability of Important New Drugs*, 80, *supra* at note 21.

²⁸⁷ U.S. General Accounting Office, *FDA can further Improve its Adverse Drug Reaction Reporting System: Report to the Secretary of Health and Human Services*, 3, *supra* at note 19.

²⁸⁸ U.S. General Accounting Office, *FDA Drug Approval: A Lengthy Process that Delays the Availability of Important New Drugs*, 80, *supra* at note 21.

²⁸⁹ Institute of Medicine (IOM), *The Future of Drug Safety: Promoting and Protecting the Health of the Public*, 49-50, *supra* at note 15.

²⁹⁰ Barry Meier, "A Call for a Warning System on Artificial Joints," *The New York Times*, sec. A, July 29, 2008.

²⁹¹ Institute of Medicine (IOM), *Evidence-Based Medicine and the Changing Nature of Health Care: 2007 IOM Annual Meeting Summary*, 132-141, *supra* at note 7.

²⁹² See Gilkich and Dreyer, *Registries for Evaluating Patient Outcomes: A User's Guide*, *supra* at note 283.

²⁹³ See Centers for Medicare and Medicaid Services, *National Coverage Determinations with Data Collection as a Condition of Coverage: Coverage with Evidence Development*, *supra* at note 240.

²⁹⁴ Institute of Medicine (IOM), *Evidence-Based Medicine and the Changing Nature of Health Care: 2007 IOM Annual Meeting Summary*, 134, *supra* at note 7.

²⁹⁵ Robert N. Hotchkiss, "A Registry for Artificial Joints," *The New York Times*, sec. Letters, August 7, 2008; Institute of Medicine (IOM), *Evidence-Based Medicine and the Changing Nature of Health Care*:

similar Philadelphia area registry were dismantled within two years of their initiation out of cost concerns.²⁹⁶ Limited budgets may directly impact the quality of these registries. Additionally, provider fears of malpractice suits may hinder their contributions to registries.²⁹⁷ In general, registries are a promising option to develop evidence, but the lack of a coordinated and targeted effort with clear long-term funding renders them currently unreliable as a permanent and ongoing source of evidence generation and assessment efforts.

2. Litigation

The significant history of "failure-to-warn" cases brought against the sponsors of prescription medical products by patients has contributed substantially to uncovering privately held evidence through the power of subpoena. Generally, failure-to-warn cases charge that sponsors are aware of new benefit-risk information that is not yet present in the labeling or advertising, and that they withheld such information from patients, thereby failing to warn them of possible risks.²⁹⁸ A former Commissioner of the FDA regarded these lawsuits as a "'feedback loop' [that] enabled the agency to better do its job," noting "the FDA has often acted in response to information that has come to light in state damages litigation after a drug has been approved."²⁹⁹

During the Bush Administration, the FDA stated that it believed that state failure-to-warn claims were pre-empted (or blocked) by federal law, and its assertions spawned new attempts to set legal precedents that would eliminate these types of lawsuits.³⁰⁰ Specifically, the FDA stated that the benefit-risk information it prescribed in the labeling constituted "both a 'floor' and a 'ceiling,'" implying that the FDA had captured all the

2007 IOM Annual Meeting Summary, 141, *supra* at note 7. See also Gilkich and Dreyer, *Registries for Evaluating Patient Outcomes: A User's Guide*, *supra* at note 283, describing the many requirements to set up a registry.

²⁹⁶ Reidenberg, *Improving how we Evaluate the Toxicity of Approved Drugs*, 2, *supra* at note 52.

²⁹⁷ Institute of Medicine (IOM), *Evidence-Based Medicine and the Changing Nature of Health Care: 2007 IOM Annual Meeting Summary*, 141, *supra* at note 7.

²⁹⁸ Kessler and Vladeck, *A Critical Examination of the FDA's Efforts to Preempt Failure-to-Warn Claims*, 462, *supra* at note 61.

²⁹⁹ *ibid.*, 463, 477, 483.

³⁰⁰ Food and Drug Administration and Department of Health and Human Services, "Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products," *Federal Register* 71, no. 15 (January 24, 2006), 3933-3936, <http://edocket.access.gpo.gov/2006/pdf/06-545.pdf>. For a historical perspective on the shift in FDA's positions, see Kessler and Vladeck, *A Critical Examination of the FDA's Efforts to Preempt Failure-to-Warn Claims*, 461-495, *supra* at note 61.

relevant knowledge within the label at any instant in the product's lifecycle.³⁰¹ Scholars argued that federal pre-emption (and the implication of a static label) would eliminate the incentives for sponsors both to develop and to disclose accurate, updated performance information that only becomes available in the postmarket.³⁰² Further, the potential elimination of state tort litigation would have restricted the use of the power to subpoena (e.g., the ability to demand company evaluations and other internal documents of the drug's performance in the market), which is a significant information-gathering tool only available via litigation.³⁰³ Subpoena power has historically revealed suppressed benefit-risk information with respect to Halcion™ (triazolam), Zomax™ (zomepirac), and ephedra.³⁰⁴ These high profile cases, and recent litigation against the manufacturers of Paxil™ (paroxetine hydrochloride), Celebrex™ (celecoxib), Baycol™ (cerivastatin), and Vioxx™ (rofecoxib) demonstrated that pharmaceutical companies withheld clinical trial data that resulted in negative outcomes concerning their products.³⁰⁵ In spring 2009, in the case of *Wyeth v. Levine*, the Supreme Court upheld the ability of plaintiffs to bring state tort claims against manufacturers of prescription drug products, negating much of the pre-emption debate.³⁰⁶

Novel legal strategies initiated by public actors have just begun to expose the depths of privately held benefit-risk information gathered by pharmaceutical companies that has been concealed from the public. First, in 2004, state governments began suing manufacturers for fraudulently representing their products by withholding clinical evidence from providers.³⁰⁷ Many of these lawsuits have ended in settlements³⁰⁸, sealing

³⁰¹ Food and Drug Administration and Department of Health and Human Services, *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, 3935, *supra* at note 300.

³⁰² Kessler and Vladeck, *A Critical Examination of the FDA's Efforts to Preempt Failure-to-Warn Claims*, 461-495, *supra* at note 61.

³⁰³ *ibid.*, 491-492.

³⁰⁴ *ibid.*, 493-495.

³⁰⁵ Fontanarosa, Rennie and DeAngelis, *Postmarketing Surveillance--Lack of Vigilance, Lack of Trust*, 2647-2650, *supra* at note 52.

³⁰⁶ *Wyeth v. Levine*, No. 06-1249, 129 (Supreme Court of the United States 2009). The majority stated, "And the FDA's newfound opinion, expressed in its 2006 preamble, that state law 'frustrate[s] the agency's implementation of its statutory mandate,' 71 Fed. Reg. 3934, does not merit deference... Indeed, the 'complex and extensive' regulatory history and background relevant to this case... undercut the FDA's recent pronouncements of pre-emption, as they reveal the longstanding coexistence of state and federal law and the FDA's traditional recognition of state-law remedies."

³⁰⁷ Gardiner Harris, "Spitzer Sues a Drug Maker, Saying it Hid Negative Data," *The New York Times*, sec. A, June 3, 2004. The civil lawsuit accused the manufacturer of consumer fraud, perpetrated by withholding

the evidence developed in court proceedings. Patient and public health advocates have argued that such practices should be illegal when public health issues are involved; this issue came to the forefront when a plaintiff's expert witness leaked information to the media to protest its legal shielding by the court.³⁰⁹ This idea continues to gain traction as more (legally) unsealed documents reveal blatant intentions to suppress negative clinical trial data.³¹⁰

In part, as a result of the leaked evidence and other unsealed documents, the federal government has been able to build federal criminal cases against manufacturers for off-label promotion.³¹¹ Federal lawsuits also have resulted when whistleblowers, usually former company employees, have documented illegal behavior and turned it over to the government, particularly the promotion of off-label uses.³¹² In 2004, there were approximately 100 whistleblower cases under seal involving allegations against over 200 drug manufacturers with respect to 500 different products.³¹³ All told, these cases, if unsealed, are likely to reveal inappropriate physician promotion and censorship of performance information. In light of the wave of lawsuits in the last five years, some scholars argue that litigation actually serves as an information creation deterrent since information disclosure is a frequent outcome of the legal system.³¹⁴ Recent increases in

the results of negative clinical studies of adolescents and the Paxil™ (paroxetine). It also accused the manufacturer of improper physician promotion for off-label uses.

³⁰⁸ See, for example, Alex Berenson, "33 States to Get \$62 Million in Zyprexa Case Settlement," *The New York Times*, sec. B, October 7, 2008.

³⁰⁹ Kris Hundley, "Drugmaker Wants to Seal Info - for You," *St. Petersburg Times*, sec. A, February 15, 2009... quoting Dr. David Egilman, the plaintiffs' witness, "Confidentiality agreements that prohibit disclosure of important information that may impact public health to state and federal authorities should be illegal. The court should at least send all discovery in drug cases to the FDA and DOJ (Department of Justice) for review if they intend to seal them."

³¹⁰ See Duff Wilson, "Drug Maker's E-Mail Released in Seroquel Lawsuit," *The New York Times*, sec. B, February 28, 2009. Emails by a company's publications manager admitted to burying the results of three clinical trials and trying to diminish the impact of negative findings on a fourth.

³¹¹ See Miriam Hill, "Lilly Fined \$1.4 Billion in Zyprexa Case," *The Philadelphia Inquirer*, sec. C, January 16, 2009.

³¹² Liz Kowalczyk, "Pfizer Unit Agrees to \$430m in Fines Division to Plead Guilty to Illegally Marketing its Top Epilepsy Drug," *The Boston Globe*, sec. D, May 14, 2004. For a legal analysis, see Edward P. Lansdale, "Used as Directed? How Prosecutors are Expanding the False Claims Act to Police Pharmaceutical Off-Label Marketing," *New England Law Review* 41 (Fall 2006), 159-198.

³¹³ Jonathan K. Henderson and Quintin Cassady, "Drug Deals in 2006: Cutting Edge Legal and Regulatory Issues in the Pharmaceutical Industry," *Annals of Health Law* 105 (Winter 2006), 107-149.

³¹⁴ Cahoy, *Medical Product Information Incentives and the Transparency Paradox*, 625-626, *supra* at note 183.

disclosure requirements for sponsors³¹⁵ in addition to public pressure to unseal documents underscore this argument.

Given the current climate, it is reasonable to believe that companies might avoid creating additional performance information other than what is required by law rather than risk unwanted disclosure. However, careful construction of policy incentives that improve on prior attempts described herein can guard against these possibilities. Litigation is an imperfect information channel and certainly not the most desirable one from a public policy standpoint. Benefit-risk information becomes available long after the harm has occurred, and so the chief role of litigation is to deter manufacturers from hiding information they have developed. It has risen in importance as a consequence of crucial gaps in postmarket evidence generation, assessment, and management.

³¹⁵ Title VII: Clinical Trial Databases in *Food and Drug Administration Amendments Act of 2007*, Public Law 110-85, codified at 42 U.S.C. § 282, requiring publication of all but Phase I clinical trials.

IV. Current State Analysis

Having reviewed the broad historical context and failed prior policies that have shaped the system of postmarket evidence development and utilization, it is important to understand why the current state presents both a renewed window of opportunity and a capacity for change. First, the interests of major stakeholders are evaluated in light of future plans to build a public health information infrastructure using postmarket data to understand and manage prescription medical product performance. Next, this chapter considers the new technological and scientific opportunities, financial opportunities, and legal/regulatory enforcement approaches that stand to motivate stakeholders to change the current state and to work toward policy responses to: 1) incomplete and imperfect information generation in the postmarket, and 2) the ineffective benefit-risk management of prescription medical products. Broadly speaking, both the creation of new legal/regulatory schemes and the public financial support for new infrastructure and new research has opened a window of opportunity for stakeholders to take action now.

A. *Key Stakeholders – What are their needs and wants?*

When discussing the development and use of evidence in the postmarket, John Eisenberg, the former Director of the AHRQ, simply states:

"Every participant in the healthcare system should care about how evidence is defined. Patients will receive services based upon how evidence is weighed, and clinicians will provide services based upon their conclusions about the evidence of effectiveness and risk. Healthcare managers, purchasers, and system leaders will make decisions based upon the evidence that certain services should be provided to the clientele that they serve, and policy makers, including judicial policy makers such as judges and juries, will weigh evidence to decide whether harm has been done because a service was or was not provided."³¹⁶

1. Government Agencies

In the last few years, several agencies that make up the DHHS have received both Congressional mandates and appropriations to create public health information infrastructure(s) designed, in full or in part, to improve the public's use of prescription medical products.³¹⁷ The DHHS, as the umbrella department, oversees coordination and

³¹⁶ J. M. Eisenberg, "What does Evidence Mean? Can the Law and Medicine be Reconciled?" *Journal of Health Politics, Policy and Law* 26, no. 2 (Apr, 2001), 373.

³¹⁷ *Food and Drug Administration Amendments Act of 2007, Public Law 110-85* and *American Recovery and Reinvestment Act of 2009, Public Law 111-5*.

resource allocation among its subordinate agencies – the FDA, the CMS, the AHRQ, and the NIH – to fulfill these mandates. The evolution of future infrastructure generates high-level interest and advocacy among stakeholders because its eventual shape will influence regulatory policy, reimbursement policy, and clinical practice. From a government agency perspective, it will also influence future budgets and staffing. It is in each subordinate agency's interest to distinguish itself from the others in the competition for resources. Consequently, these agencies may resist efforts to combine evidence generation mandates into a new agency or to shift responsibilities among themselves.

Potential inter-governmental turf battles aside, historically (with the possible exception of the NIH), these public health agencies have struggled to maintain the integrity of their scientific and research pursuits in the face of strong, politically powerful, and well-connected stakeholder groups that have much to gain or lose as a result of agency action. These agencies typically require the cooperation of such groups in order to receive specialized advice to aid in scientific decision-making. However, in so doing, the agencies risk their reputation as science-based, objective, fair, and unbiased. Indeed, executive agencies are delegated various administrative lawmaking powers by Congress precisely because they function as expert bodies and are deemed more suited to enacting law or regulations in their specialty.³¹⁸

Extramural research programs enhance the credibility of these pursuits and theoretically avoid conflicts of interest. Also, the expanded use of advisory committees underscores agency efforts.³¹⁹ As an example of their now pervasive input to science and technology issues, Congress has mandated that all new molecular entities (i.e., truly innovate products) be referred to advisory committees prior to approval.³²⁰ However, potential financial and intellectual conflicts of interest among advisory committee

³¹⁸ See Stephen G. Breyer and Richard B. Stewart, *Administrative Law and Regulatory Policy* (Boston: Little, Brown, 1979).

³¹⁹ Institute of Medicine (IOM), *Food and Drug Administration Advisory Committees*, eds. Richard A. Rettig, Laurence E. Earley and Richard A. Merrill (Washington, D.C.: National Academy Press, 1992), Chapter 2. See generally, Sheila Jasanoff, *The Fifth Branch: Science Advisers as Policymakers* (Cambridge, Mass.: Harvard University Press, 1990).

³²⁰ Sec. 918: Referral To Advisory Committee in *Food and Drug Administration Amendments Act of 2007*, *Public Law 110-85*, codified at 21 U.S.C. § 355(s).

members have generated considerable attention in recent years, and have diminished the reputation of these advisory committees to act as neutral, technical advisors.³²¹

On the whole, there are few structures in place to protect or insulate the public health agencies from external influences. Historically, both the FDA³²² and the AHRQ³²³ have been subject to political retribution exercised through Congress's power of the purse and the President's Office of Management and Budget. Executive level positions in all of DHHS's subordinate agencies are political appointments and thus, it is hard to make the case that the leadership of these "scientific agencies" is as objective or neutral as might be ideal. None are constituted with deliberate legislative measures to preserve their independence, such as fixed appointment terms that avoid the political cycle, bi-partisan commission-like structures, or special procedural mechanisms that protect the head of the agency from a termination of duties for political reasons. A review of agency-specific interests is discussed next.

i. FDA

The FDA has a firm public responsibility to develop postmarket evidence on prescription medical products in order to manage the benefits and risks of these therapies. The PDUFA era significantly reprioritized the FDA's orientation, operations, and funding in ways that favored premarket review activities at the expense of postmarket efforts. Recall that budgetary mechanisms in the legislation forced the FDA to maintain fixed levels of spending in premarket activities to ensure that user fee funds were available.³²⁴ Consequently, the FDA shifted funding away from postmarket activities to meet those goals.³²⁵ The percentage of FDA funds spent on non-user fee activities (and in part, postmarket evidence evaluation) declined from 83% to 71% of the FDA's budget from

³²¹ P. Lurie and others, "Financial Conflict of Interest Disclosure and Voting Patterns at Food and Drug Administration Drug Advisory Committee Meetings," *Journal of the American Medical Association* 295, no. 16 (Apr 26, 2006), 1921-1928.

³²² Hilts, *Protecting America's Health: The FDA, Business, and One Hundred Years of Regulation*, 210-223, 325-337, *supra* at note 65.

³²³ Gray, Gusmano and Collins, *AHCPR and the Changing Politics of Health Services Research*, W3-283-307, *supra* at note 35.

³²⁴ Deborah G. Parver, "Expediting the Drug Approval Process: An Analysis of the FDA Modernization Act of 1997," *Administrative Law Review* 51 (1999), 1249, 1258-59, n62; U.S. General Accounting Office, *Food and Drug Administration: Effect of User Fees on Drug Approval Times, Withdrawals, and Other Agency Activities*, 14, *supra* at note 132.

³²⁵ *ibid.*, 3, 14. Recall that the first two cycles of PDUFA (1992-2002) specifically prohibited user fees from contributing to these activities.

1992 to 2000.³²⁶ Likewise, the staff was reduced from 86% to 74% of the FDA's workforce while staff dedicated to user-fee supported activities increased from 14 to 26%.³²⁷ The FDA's credibility suffered, and the "revolving door" phenomenon - when agency personnel depart for jobs more financially and personally rewarding in industry - was particularly acute.³²⁸ Over time, the FDA has lost the prestige, credibility, and salary opportunities needed to attract the highest quality personnel, particularly scientists and epidemiologists.³²⁹ Efforts to correct this situation have been complicated by a multi-level hiring process, but are beginning to be corrected.³³⁰

Technologically, the FDA also has much work to do. The GAO and Inspector General have repeatedly documented deficiencies in the FDA's computer systems, contributing to the poor performance of the spontaneous reporting systems and management of postmarket commitments. Congress first discovered the problem in 1982 after the drug Zomax™ (zomepirac sodium) remained on the market long after severe adverse drug reactions and deaths were reported.³³¹ Twenty-five years later, the same technological shortfalls persist. The IOM concluded that the FDA's information technology systems are "antiquated."³³² The Inspector General twice investigated and reported that the FDA had significant data management problems.³³³ Particularly, it could not identify whether or at what rate postmarket study commitments were being met, and one third of the required status reports from manufacturers were missing or

³²⁶ *ibid.*, 15.

³²⁷ *ibid.*, 15.

³²⁸ Department of Health and Human Services Office of the Inspector General, *FDA's Review Process for New Drug Applications: A Management Review*, OEI-01-01-00590 (Washington, DC: OIG, 2003), 9, 12, 45...noting that "26 percent of CDER's employees went to private industry in FY 2000 and 24 percent in FY 2001." Additionally, "leaving the FDA for a position in private industry was the most common reason for leaving the agency."

³²⁹ Food and Drug Administration, *FDA Science and Mission at Risk: Report of the Subcommittee on Science and Technology*, 33-45, *supra* at note 171.

³³⁰ Food and Drug Administration, "FDA Embarks on Major Hiring Initiative for its Public Health Mission," FDA, <http://www.fda.gov/bbs/topics/NEWS/2008/NEW01829.html>... "Biologists, chemists, medical officers, mathematical statisticians and investigators are among the experts in demand as the U.S. Food and Drug Administration begins a multi-year hiring initiative."

³³¹ See U.S. House Committee on Government Operations and Intergovernmental Relations and Human Resources Subcommittee, *FDA's Regulation of Zomax*, *supra* at note 255.

³³² Institute of Medicine (IOM), *The Future of Drug Safety: Promoting and Protecting the Health of the Public*, 202, *supra* at note 15.

³³³ See Department of Health and Human Services Office of the Inspector General, *FDA's Monitoring of Postmarket Study Commitments*, *supra* at note 264; Department of Health and Human Services Office of the Inspector General, *Postmarketing Studies of Prescription Drugs*, *supra* at note 262.

incomplete.³³⁴ In general, these types of reports underscore the significant challenges ahead in harnessing technological infrastructure for postmarket evidence development and analysis.

Since the Vioxx™ (rofecoxib)³³⁵ and SSRI³³⁶ Congressional hearings, the FDA has been publicly admonished for failing 1) to gather actionable information to prevent harms before they occur; 2) to evaluate that information in a transparent and reproducible manner; 3) to engage in risk management policies that are routinely effective; and 4) to communicate information on emerging risks and benefits to providers and patients. Shortly after the landmark 2006 IOM study³³⁷, the agency again was embarrassed when a clinical researcher - rather than the FDA staff - first identified a potentially significant postmarket risk associated with a widely prescribed therapeutic.³³⁸ The FDA's public disagreement on the issue during an advisory committee meeting did little to reassure the public on its reputation for seriously investigating safety concerns and it highlighted the contentious relationship between the premarket and postmarket divisions.³³⁹

Since then, the FDA has asserted its intention to remedy its deficiencies by using Congressional monies to build a Sentinel system³⁴⁰ to monitor medical product risk in the postmarket through new data collection and analysis mechanisms. With regard to the traditional mechanisms (spontaneous reporting and postmarket studies), the new regulatory powers enabled by the Food and Drug Administration Amendments Act

³³⁴ Department of Health and Human Services Office of the Inspector General, *FDA's Monitoring of Postmarket Study Commitments*, 11-17, *supra* at note 264.

³³⁵ U.S. Senate Committee on Finance, *FDA, Merck, and Vioxx: Putting Patient Safety First?*, *supra* at note 23.

³³⁶ U.S. House Committee on Energy and Commerce and Subcommittee on Oversight and Investigations, *FDA's Role in Protecting the Public Health: Examining FDA's Review of Safety and Efficacy Concerns in Anti-Depressant Use by Children*, *supra* at note 22.

³³⁷ Institute of Medicine (IOM), *The Future of Drug Safety: Promoting and Protecting the Health of the Public*, *supra* at note 15.

³³⁸ S. E. Nissen and K. Wolski, "Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes," *The New England Journal of Medicine* 356, no. 24 (Jun 14, 2007), 2457-2471. Although many sought to diminish the results at the time, subsequent Congressional investigations have found that the sponsor's own data did not substantially disagree with the researcher's analysis. See Alicia Mundy and Jared Favole, "Glaxo's Emails on Avandia Reveal Concern," *The Wall Street Journal*, sec. B, January 14, 2009.

³³⁹ Gardiner Harris, "F.D.A. Panel Votes to Keep Diabetes Drug on Market," *The New York Times*, June 30, 2007... "The disagreements within the F.D.A. affected almost every aspect of the hearing."

³⁴⁰ U.S. Department of Health and Human Services, Food and Drug Administration, *The Sentinel Initiative: A National Strategy for Monitoring Medical Product Safety*, 4, *supra* at note 26. The intended system "enables linking to electronic data that can be queried and analyzed in accordance with appropriate security and privacy safeguards."

(FDAAA) of 2007 are just beginning to be implemented, and so there is significant potential (and expectation) that the agency will correct historical shortcomings and start anew.

ii. AHRQ

Like the FDA, the AHRQ has been no stranger to politization by external forces. Shortly after its creation as the AHCPR in 1989, it was nearly eliminated in 1994 and then overhauled in 1999.³⁴¹ During its first brush with Congressional politics, it became a target for the Republican majority, who were displeased with the agency's role in the Clinton healthcare reform:

“The agency is supposed to support research and information dissemination on health care services and technology, medical effectiveness, and patient outcomes, but *performed an advocacy role in the health care debate* the past 2 years while its funding increased from \$125 million in 1992 to \$163 million in 1994.”³⁴² (emphasis added)

Their objection was to the mixture of objective, science-based functions with subjective and substantive policymaking; the AHCPR had ventured too far beyond the confines of an expert agency and arbiter of technical advice. Another source of strife was the fact that one of the agency's primary functions was clinical guideline development and dissemination, a role shared with specialty medical associations.³⁴³ Because the development of clinical guidelines quickly created losers and winners among medical constituencies, the AHCPR's actions produced powerful enemies.³⁴⁴ In an effort to survive, the AHCPR became the AHRQ by eliminating policy from its mission (and its name) and by funding external "evidence-based practice centers" to review evidence.³⁴⁵ These changes diffused tensions and provided political cover since academic research institutions largely inherited clinical guidelines production. By severing its policy arm and becoming the lead agency on healthcare quality, the AHRQ sought to remake its image as a scientific and non-partisan evidence clearinghouse.

³⁴¹ Eisenberg, *The Agency for Healthcare Research and Quality: New Challenges, New Opportunities*, xi-xvi, *supra* at note 34.

³⁴² C. N. Kahn 3rd, "The AHCPR After the Battles," *Health Affairs* 17, no. 1 (Jan-Feb, 1998), 109-110.

³⁴³ Gray, Gusmano and Collins, *AHCPR and the Changing Politics of Health Services Research*, W3-283-307, *supra* at note 35.

³⁴⁴ *ibid.*, w3-297... "AHCPR was also confronted in 1995 with an advocacy organization's active efforts to get it defunded. The source was an association of back surgeons who disagreed with conclusions reached by the [research group] on low-back pain and with practice guidelines based on that work."

³⁴⁵ *ibid.*

Following this second near-death experience, AHRQ's budget remained flat for several years.³⁴⁶ Traditionally, it has been more than three orders of magnitude less than the NIH's basic biomedical research budget. With the enactment of appropriations from the 2009 stimulus bill, the AHRQ's budget has nearly doubled and up to \$3 million in new hires is allocated for an expanded Effective Health Care program.³⁴⁷ Accordingly, the AHRQ's potential influence in research on prescription medical products has shifted; the extent to which its identity will be elevated as a result of these allocations is still unknown. It is unclear what role the AHRQ will play in the Federal Coordinating Council for Comparative Effectiveness Research although it has a seat at the table along with representatives from each of its sister agencies.³⁴⁸ Notably, the AHRQ is not designated as the head agency to manage this council despite its historical role and responsibility for comparative effectiveness research.

iii. CMS

Via the CMS, the federal government finances a significant portion of medical care, which accounts for more than a third of all healthcare spending in the U.S.³⁴⁹ Additionally, it acts as a standard-setter in its coverage decisions for public payors (i.e., the Veterans Health Administration and the Department of Defense) and private payors.³⁵⁰ As a steward of taxpayer funds, it has an interest in making the best choices regarding the safety, clinical effectiveness, and cost effectiveness of therapeutic interventions involving prescription medical products.³⁵¹ However, its efforts to make these choices based on a sound evidence base have met up against strong resistance from

³⁴⁶ See Department of Health and Human Services, "Federal Coordinating Council for Comparative Effectiveness Research Membership," DHHS, <http://www.hhs.gov/recovery/programs/os/cerbios.html> (accessed April 14, 2009).

³⁴⁷ See Title VIII: Departments of Labor, Health and Human Services, and Education, and Related Agencies in *American Recovery and Reinvestment Act of 2009, Public Law 111-5*.

³⁴⁸ Sec. 804: Federal Coordinating Council for Comparative Effectiveness Research in *American Recovery and Reinvestment Act of 2009, Public Law 111-5*.

³⁴⁹ Centers for Medicare and Medicaid Services, "National Health Expenditure Data: NHE Fact Sheet," CMS, http://www.cms.hhs.gov/NationalHealthExpendData/25_NHE_Fact_Sheet.asp (accessed April 24, 2009).

³⁵⁰ Carnahan, *Medicare's Coverage with Study Participation Policy: Clinical Trials Or Tribulations?*, 235, *supra* at note 75.

³⁵¹ U.S. Congressional Budget Office, *Research on the Comparative Effectiveness of Medical Treatments: Issues and Options for an Expanded Federal Role*, 2, *supra* at note 6.

physician groups³⁵² and the industry³⁵³, who fear that findings of insufficient evidence will result in the loss of coverage. The CMS's forty-year long battle to define "reasonable and necessary" underscores this difficulty.³⁵⁴ Its latest attempt to link information to coverage was announced in 2005: the coverage with evidence development (CED) policy, which guaranteed Medicare coverage of specific promising technologies *conditioned on* patient participation in a registry or clinical trial.³⁵⁵ Despite its history of fits and starts in coverage policy, the CMS has an influential role in the risk management of prescription medical products through the use of reimbursement incentives and prior authorization policies that influence access. Its need for evidence to generate national coverage decisions underscores its keen interest in future public health information infrastructure.

2. Patients

Patients obviously have a significant interest in their health and the health of others, if for no other reason than the partially taxpayer funded healthcare system. However, it is unclear if they are generally aware of imminent plans by public agencies³⁵⁶ to design public health information infrastructures that will rely, in part, on the ability to query various databases of identifiable patient data in order to gain knowledge on the postmarket performance of medical products.³⁵⁷ Further, it is uncertain whether patients understand that compiling longitudinal case reports or studies may sometimes require

³⁵² For example, see Tunis and Pearson, *Coverage Options for Promising Technologies: Medicare's 'Coverage with Evidence Development'*, 1220-1222, *supra* at note 236...discussing the CMS's decision to conduct a clinical trial on Lung Volume Reduction Surgery (LVRS) and the vigorous opposition to it from some Congressional representatives and provider representatives.

³⁵³ Jonathan D. Salant and Aliza Marcus, "Drugmakers Boost Lobbying to Police Drug Comparisons (Update1)," *Bloomberg.com*, April 17, 2009, <http://www.bloomberg.com/apps/news?pid=20601109&sid=aHjr0BP1zvgo&refer=news>.

³⁵⁴ See Carnahan, *Medicare's Coverage with Study Participation Policy: Clinical Trials Or Tribulations?*, 243-258, *supra* at note 75; Kinney, *Medicare Coverage Decision-Making and Appeal Procedures: Can Process Meet the Challenge of New Medical Technology?*, 1471-1482, *supra* at note 78; Foote, *Why Medicare Cannot Promulgate a National Coverage Rule: A Case of Regula Mortis*, 707-730, *supra* at note 80.

³⁵⁵ Tunis and Pearson, *Coverage Options for Promising Technologies: Medicare's 'Coverage with Evidence Development'*, 1218-1230, *supra* at note 236.

³⁵⁶ U.S. Department of Health and Human Services, Food and Drug Administration, *The Sentinel Initiative: A National Strategy for Monitoring Medical Product Safety*, 24, *supra* at note 26.

³⁵⁷ See remarks in Food and Drug Administration, eHealth Initiative Foundation and Brookings Institute, "Sentinel Initiative: Structure, Function, and Scope" (Washington, DC, FDA, December 16, 2008), <http://www.fda.gov/oc/initiatives/criticalpath/transcript121608.pdf>.

private data holders to exchange protected health information in order to link a single patient across multiple databases.³⁵⁸ These queries fall under the public health surveillance exception of the Privacy Rule and so generally will not require individual patient authorization although this status may be uncertain if formal research studies are initiated as a result of the queries.³⁵⁹

While these public health exceptions may be easily justified for infectious disease prevention or to report cases of child abuse, the public has yet to be confronted by more routine monitoring of data for safety and effectiveness questions that are less time-sensitive and may appear initially to be overly broad. Yet, these are precisely the types of postmarket evidence questions that currently go unanswered (e.g., what are the most effective options in chronic care for osteoporosis). A balance exists between an individual notion of privacy rights with regard to secondary uses of health data and the potential impediment to postmarket evidence development if consent is required for a majority of surveillance questions.³⁶⁰

To illustrate, small national surveys conducted in 2005 indicated that 79% of respondents rated the ability to consent various entities for use of their records as a high priority in the design of future electronic health record networks.³⁶¹ Additional surveys in 2006 showed that some Americans would be willing to allow certain secondary uses of their data, but are concerned that their data would be marketed without their consent.³⁶²

³⁵⁸ Evans, *Congress' New Infrastructural Model of Medical Privacy*, 606, *supra* at note 55. However, work is being done to design computer algorithms that permit linking of patient records without identifying the actual patients. See J. Jonas, "Identity Resolution: 23 Years of Practical Experience and Observations at Scale" ACM (New York, NY, USA, 2006).

³⁵⁹ Evans, *Congress' New Infrastructural Model of Medical Privacy*, 597-598, *supra* at note 55.

³⁶⁰ *ibid.*, 606-608. For more on potential policy options and balance of interests, see Center for Democracy and Technology, "Rethinking the Role of Consent in Protecting Health Information Privacy," Center for Democracy and Technology, <http://www.cdt.org/healthprivacy/200910126Consent.pdf> (accessed April 15, 2009).

³⁶¹ Markle Foundation, "Attitudes of Americans regarding Personal Health Records and Nationwide Electronic Health Information Exchange," Markle Foundation, http://www.phrconference.org/assets/research_release_101105.pdf (accessed April 17, 2009).

³⁶² Lake Research Partners, American Viewpoint and Markle Foundation, "Survey Finds Americans Want Electronic Personal Health Information to Improve Own Health Care," Markle Foundation, http://www.markle.org/downloadable_assets/research_doc_120706.pdf (accessed April 17, 2009)... "A majority of Americans would be willing to share their information with their identity protected for a number of uses, including sharing information with public health officials to detect disease outbreaks (73%)... or with researchers, doctors, and hospitals to learn how to improve quality of care (72%)... However, when asked, most Americans say they want to have some control over the use of their information for these purposes."

Public agencies are obligated to safeguard patient data and to use it parsimoniously when pursuing public health questions of importance, but some scholars have raised the notion that patient data – once connected in time and space across owners – will become increasingly valuable, and temptations to sell packaged data in order to sustain an infrastructure are possible.³⁶³ As a new public health information infrastructure is designed and the public becomes more aware of its uses, it will become increasingly important to engage in dialogue at public meetings and in oversight committees. The proposed public health information infrastructure is primarily a public good. As patients, we are all part-owners of such an infrastructure. Its implementation requires active public engagement to reach consensus on designs that respect patient concerns related to the privacy and security of their data.

One thing that patients will seek to gain from a public health information infrastructure is to ensure that *their questions* on the various treatments available are considered. Patients are inundated with new medical treatments, and yet, vary widely in their health literacy and numeracy.³⁶⁴ Much of their information is garnered from DTCA, and these campaigns may affect their expectations and treatment preferences.³⁶⁵ Patient-provider relationships have evolved significantly away from provider-directed, asymmetrical decision-making to shared decision-making in which providers are expected to explain and interpret the best available evidence on potential treatments.³⁶⁶ Yet, empirical studies have shown that providers do not routinely communicate

³⁶³ Evans, *Congress' New Infrastructural Model of Medical Privacy*, 607-608, *supra* at note 55.

³⁶⁴ T. C. Davis and others, "Low Literacy Impairs Comprehension of Prescription Drug Warning Labels," *Journal of General Internal Medicine* 21, no. 8 (Aug, 2006), 847-851; T. C. Davis and others, "Literacy and Misunderstanding Prescription Drug Labels," *Annals of Internal Medicine* 145, no. 12 (Dec 19, 2006), 887-894; E. Peters and others, "Numeracy Skill and the Communication, Comprehension, and Use of Risk-Benefit Information," *Health Affairs* 26, no. 3 (May-Jun, 2007), 741-748.

³⁶⁵ J. M. Donohue, M. Cevalco and M. B. Rosenthal, "A Decade of Direct-to-Consumer Advertising of Prescription Drugs," *The New England Journal of Medicine* 357, no. 7 (Aug 16, 2007), 673-681.; R. L. Kravitz and others, "Influence of Patients' Requests for Direct-to-Consumer Advertised Antidepressants: A Randomized Controlled Trial," *Journal of the American Medical Association* 293, no. 16 (Apr 27, 2005), 1995-2002.

³⁶⁶ Institute of Medicine (IOM), *Knowing what Works in Health Care: A Roadmap for the Nation*, 2... "The era of physician as sole health care decision maker is long past." See also S. H. Woolf and others, "Promoting Informed Choice: Transforming Health Care to Dispense Knowledge for Decision Making," *Annals of Internal Medicine* 143, no. 4 (Aug 16, 2005), 293-300. For a counterperspective, compare W. Levinson and others, "Not all Patients Want to Participate in Decision Making. A National Study of Public Preferences," *Journal of General Internal Medicine* 20, no. 6 (Jun, 2005), 531-535.

uncertainty about evidence to patients.³⁶⁷ Further, the manner or frame in which benefits and risks are communicated (e.g., absolute risk v. relative risk, benefits presented first or last) can bias patient perception.³⁶⁸ In general, researchers have documented knowledge gaps in the optimal methods (e.g., graphical or numeric) for communicating various types of uncertainty to patients, the limitations of applying population-based benefit-risk information to individual patients (or tailoring health information), and the tradeoff between full disclosure and patient processing capability.³⁶⁹ Much work must be done to translate the language of uncertainty - largely probabilistic mathematics and statistics - into a language of actionable decision points in which patients clearly understand the breadth of their options and the known uncertainties in light of their preferences.

Additionally, patients may have trouble coping with dynamic information states as evidence-based emergent science is generated. The normal scientific process, which involves the evolution of scientific paradigms³⁷⁰ as hypotheses are tested, rejected, refined, and refuted may be foreign to patients. To the layman, the changing nature of science may appear as simply confusion or worse, mistakes rooted in incompetence. Patients may have interpreted FDA approval or insurance coverage reimbursement as signals that guarantee the safety and effectiveness of prescription medical products under most circumstances.³⁷¹ However, media coverage and Congressional inquiries into high profile regulatory failures have most likely influenced the noted dips in public confidence.³⁷²

³⁶⁷ For a summary of studies, see M. C. Politi, P. K. Han and N. F. Col, "Communicating the Uncertainty of Harms and Benefits of Medical Interventions," *Medical Decision Making* 27, no. 5 (Sep-Oct, 2007), 681-682.

³⁶⁸ J. E. Hux and C. D. Naylor, "Communicating the Benefits of Chronic Preventive Therapy: Does the Format of Efficacy Data Determine Patients' Acceptance of Treatment?" *Medical Decision Making* 15, no. 2 (Apr-Jun, 1995), 152-157.

³⁶⁹ Politi, Han and Col, *Communicating the Uncertainty of Harms and Benefits of Medical Interventions*, 691-692, *supra* at note 367.

³⁷⁰ For theory on the evolution of scientific paradigms, see Thomas S. Kuhn, *The Structure of Scientific Revolutions* (Chicago: University of Chicago Press, 1962).

³⁷¹ Even industry executives acknowledge that they may have contributed to the perception problem, specifically that "direct-to-consumer advertising lulled many Americans into thinking that taking prescription drugs was as safe as eating candy." See Avery Johnson and Ron Winslow, "Side Effect: Drug Makers Say FDA Safety Focus is Slowing New-Medicine Pipeline," *The Wall Street Journal*, sec. A, June 30, 2008.

³⁷² Food and Drug Administration, *FDA Science and Mission at Risk: Report of the Subcommittee on Science and Technology*, B-7, *supra* at note 171.

Patients and patient groups can play a critical role in their care by insisting on a consideration of the available evidence when choosing among therapeutic options, and advocating for the development of better evidence (including volunteering for studies and consenting their data for public health uses) when shortcomings exist. Coordinated disease-centered patient groups, like the Cystic Fibrosis Foundation and PXE International, have played a significant role in evidence development for treatments that directly affected their care.³⁷³ These interest groups tend to be small, homogeneous, tight-knit and focused on development of novel premarket treatments. They are qualitatively different from the more routine set of patients suffering from diabetes, obesity, or hypertension. These patients are diffuse and less likely to form aggressive interest groups to challenge the levels of evidence associated with particular treatments.³⁷⁴ Additionally, when multiple treatments exist and the perceived risk of trial and error in medication selection is low, patients may experiment rather than coordinate to demand systematic studies to highlight the best options. Patient advocacy in these chronic care areas is *especially necessary*, and likely to invoke the thorny privacy issues described above.

3. Providers

Currently, providers lack a user-friendly system that supports their capacity to stay abreast of emerging postmarket information on prescription medical product performance and that responds to healthcare delivery questions that directly impact their daily decisions. A public health information infrastructure will be of interest to them if it can help close that gap by providing actionable information without significant time spent searching for answers. In time-constrained environments, providers have noted difficulty managing information.³⁷⁵ Psychological studies have shown that when individuals face obstacles in processing information, they fall back on heuristics, recent experiences, and

³⁷³ Alan Stockdale and Sharon F. Terry, "Advocacy Groups and the New Genetics" In *The Double-Edged Helix: Social Implications of Genetics in a Diverse Society*, ed. Joseph S. Alper (Baltimore, Md.: Johns Hopkins University Press, 2002), 80-101.

³⁷⁴ For more on the political theory that supports this notion, see Mancur Olson, *The Logic of Collective Action; Public Goods and the Theory of Groups* (Cambridge, MA: Harvard University Press, 1965).

³⁷⁵ Institute of Medicine (IOM), *Knowing what Works in Health Care: A Roadmap for the Nation*, 36, *supra* at note 366... "For physicians—and patients—who are motivated enough to read through and assess all of the relevant individual clinical studies on their own, keeping current is an arduous, if not impossible, task." See also Eisenberg, *What Does Evidence Mean? Can the Law and Medicine be Reconciled?*, 370, *supra* at note 316... "The average physician is said to read scientific journals approximately two hours per week, and most are likely overwhelmed by the volume of material confronting them."

other processes that may be subject to cognitive flaws.³⁷⁶ Limited biostatistics training during medical school is an additional barrier although numerous academic medical organizations have created grading systems to help interpret evidence quality.³⁷⁷ These grading systems put a premium on randomized controlled trials, which are not planned as the primary source of postmarket evidence in current infrastructure models. Consequently, it remains to be seen whether providers will "trust" data obtained through observational or epidemiologic means and incorporate it into their practices.³⁷⁸

In large part, journal articles are still the bread and butter of medical evidence publication and providers may be more accepting of postmarket evidence results that are published formally in addition to some form of emergent communications. It is important to note that competing information sources on prescription medical products are available from detail personnel or salesmen within the industry.³⁷⁹ Much of this information is conveyed through the use of carefully selected journal reprints, many of which highlight the positive outcomes on prescription medical products while suppressing negative outcomes. While studies have shown that the medical literature generally suffers from this form of selective publication bias³⁸⁰, it is augmented by typical journal reprint practices.

Since the delivery of healthcare services has shifted permanently to evidence-based medicine practices, physician constituencies are likely to be particularly interested in how the development of evidence affects their ability to practice, the need for their services, and their liability risks in terms of what emergent information they will be expected to

³⁷⁶ Lars Noah, "Medicine's Epistemology: Mapping the Haphazard Diffusion of Knowledge in the Biomedical Community," *Arizona Law Review* 44 (Summer 2002), 376.

³⁷⁷ See, for example, G. H. Guyatt and others, "GRADE: An Emerging Consensus on Rating Quality of Evidence and Strength of Recommendations," *British Medical Journal* 336, no. 7650 (Apr 26, 2008), 924-926; Agency for Healthcare Research and Quality, "U.S. Preventive Services Task Force Grade Definitions," AHRQ, <http://www.ahrq.gov/clinic/uspstf/grades.htm> (accessed April 24, 2009).

³⁷⁸ Noah, *Medicine's Epistemology: Mapping the Haphazard Diffusion of Knowledge in the Biomedical Community*, 385-396, *supra* at note 376.

³⁷⁹ See S. H. Podolsky and J. A. Greene, "A Historical Perspective of Pharmaceutical Promotion and Physician Education," *Journal of the American Medical Association* 300, no. 7 (Aug 20, 2008), 831-833; E. G. Campbell and others, "A National Survey of Physician-Industry Relationships," *The New England Journal of Medicine* 356, no. 17 (Apr 26, 2007), 1742-1750; D. Blumenthal, "Doctors and Drug Companies," *The New England Journal of Medicine* 351, no. 18 (Oct 28, 2004), 1885-1890.

³⁸⁰ Lee, Bacchetti and Sim, *Publication of Clinical Trials Supporting Successful New Drug Applications: A Literature Analysis*, e191; Rising, Bacchetti and Bero, *Reporting Bias in Drug Trials Submitted to the Food and Drug Administration: Review of Publication and Presentation*, e217; discussion e217, both *supra* at note 86.

know and employ. They may want reassurance on how such a public health information infrastructure might affect pay-for-performance initiatives and other quality ratings. Providers (including nurses and pharmacists) will also most likely be primary data entry points for electronic health record data, which may later be utilized in a public health information infrastructure, and so consideration of what data are needed and how it will be collected affects their workflow.³⁸¹ For instance, some physicians have advanced the idea that a new infrastructure system would be more robust if it was built around a provider's normal work routines.³⁸² In general, there is still a wide variance in terms of adoption of electronic health records³⁸³ and other new media tools such as text alerts, social networking, and other communication devices among providers. It is clear that multiple communication approaches between public health agencies and providers will be necessary.

Finally, providers will want to understand how a public health information infrastructure will affect their relationship with patients, particularly with respect to the level of information that patients will receive. Providers treat a wide variety of patients with differing communication needs, wants, and cognitive capabilities with regard to evidence on prescription medical products. Whatever the patient's preferences, a provider has a vested interest in providing him or her the best care – which includes a provider's judgment on applicable knowledge generated through a public health information infrastructure - and in clearly communicating that knowledge to the patient. A recent IOM panel found that there is much work to be done in this area:

"Physicians tend to underestimate the amount of information that patients want, control discussions and discourage patient involvement, overestimate how much patients know, overestimate the efficacy with which they accomplish important communication tasks (how well they have communicated information to their patients), and have limited time."³⁸⁴

³⁸¹ See comments in Institute of Medicine (IOM), *Learning Healthcare System Concepts v2008: Annual Report*, 32, *supra* at note 57... "One starting point is anchoring the focus of clinical effectiveness research planning and priority setting at the point of service—the patient-provider interface—as the source of attention, guidance, and involvement in defining the key questions to engage."

³⁸² Reidenberg, *Improving How we Evaluate the Toxicity of Approved Drugs*, 1-2, *supra* at note 52.

³⁸³ A. K. Jha and others, "Use of Electronic Health Records in U.S. Hospitals," *The New England Journal of Medicine* 360, no. 16 (Apr 16, 2009), 1628-1638.

³⁸⁴ Institute of Medicine (IOM), *Understanding the Benefits and Risks of Pharmaceuticals: Workshop Summary*, 32, *supra* at note 9.

4. Industry

The industry has an interest in a) extending patent life through exclusivities or other means, b) generating a broad patient and provider base for their prescription medical products, and c) continually bringing new products to market to sustain the impending loss of patent on blockbuster drugs. Like the FDA, in the last five years, biopharmaceutical companies have lost face with the American public as their efforts to hide important public health information have been exposed.³⁸⁵ Following a series of high-profile court cases and settlements, it is clear that corporate actors willfully withheld or downplayed negative information either developed or confirmed in the postmarket³⁸⁶, and in some cases, continue to try to do so.³⁸⁷ In 2005, Billy Tauzin, head of the trade industry association, was quoted as saying "The industry has found, I think correctly so, that the country has come to resent our industry."³⁸⁸

Bad behavior aside, failing to act on known benefit-risk information is a poor long-term business model and represents companies that are slow to innovate. As it is, the high cost of drug development often results in risk-averse development choices that favor creating new formulations (dosages) of a drug, combining two already approved drugs, or

³⁸⁵ Public opinion polls have noted that the pharmaceutical industry has a positive ranking among a quarter of Americans. Additionally, when the public was polled on whether a certain industry was trustworthy, only 13% of Americans ranked pharmaceutical companies as trustworthy in 2003 and 7% in 2006. See Harris Interactive, "Healthcare Industries Still Amongst most Popular Targets for More Regulation but Support for Regulation Declines for Third Year in a Row," *Harris Interactive Healthcare News* 6, no. 8 (2006), http://www.harrisinteractive.com/news/newsletters/healthnews/HI_HealthCareNews2006Vol6_Iss08.pdf; Harris Interactive, "The 9th Annual RQ: Reputations of the 60 most Visible Companies. A Survey of the U.S. General Public." Harris Interactive, http://www.harrisinteractive.com/news/mediaaccess/2008/HI_BSC_REPORT_AnnualRQ_USASummary07-08.pdf (accessed April 14, 2009).

³⁸⁶ See, for example, comments in Fontanarosa, Rennie and DeAngelis, *Postmarketing Surveillance--Lack of Vigilance, Lack of Trust*, 2647-2650, *supra* at note 52; Harris, *Spitzer Sues a Drug Maker, Saying it Hid Negative Data*, *supra* at note 307; Mundy and Favole, *Glaxo's Emails on Avandia Reveal Concern*, *supra* at note 338; Hill, *Lilly Fined \$1.4 Billion in Zyprexa Case*, *supra* at note 311.

³⁸⁷ Hundley, *Drugmaker Wants to Seal Info - for You*, *supra* at note 309... Lawyers for sponsors claimed, "This [disclosure] could jeopardize public safety by causing confusion and alarm in patients, who may then discontinue their medication without seeking the guidance of a medical professional." This line of argument – that patients are incapable of making logical decisions about their health - is unfortunately too common and comes from the same sources who rally against the "paternalist" FDA.

³⁸⁸ Todd Zwillich, "Drug Industry Pledges New Openness: Head of Lobbying Group Says He Wants to Regain Trust," *WebMD Health News*, May 3, 2005, <http://www.webmd.com/news/20050503/drug-industry-pledges-new-openness>.

other type of "line extensions."³⁸⁹ Second, the exclusivity provisions of the Hatch-Waxman Act, which extend the period of time during which an original manufacturer can prevent generic entry, incentivize incremental improvements via modified formulations.³⁹⁰ The drug rebate system used by the CMS also creates incentives to modify existing drugs.³⁹¹ All told, these incentives combined with the reluctance of biopharmaceutical companies to take action on data generated in the postmarket do not encourage innovation.

Postmarket data permit industry (among others) to monitor performance and assess limitations. These activities should inform future development by both allowing industry to discontinue its investment in ineffective products and to discover unmet needs.³⁹² To illustrate a postmarket monitoring success story, Tysabri™ (natalizumab), a medication for multiple sclerosis, was removed from the market shortly after it was approved when it was linked to a rare and fatal viral condition known as progressive multifocal leukoencephalopathy (PML).³⁹³ However, because of its significant therapeutic value, the FDA and the sponsor worked together to resume marketing under a restricted distribution program that closely monitors every patient, provider, and facility that uses, prescribes, or dispenses the medication.³⁹⁴ This program is an example of a performance-linked access system and is part of a risk management plan in place to detect early symptoms of a possible adverse drug reaction and to promptly remove patients from therapy.³⁹⁵ While this type of monitoring is resource-intensive, it was the mechanism that *allowed the company to get a return on its investment* and is an example of the means by which promising and risky pharmaceutical innovations can be securely managed.

Having realized such postmarket risk management features are a permanent part of

³⁸⁹ Wood, *A Proposal for Radical Changes in the Drug-Approval Process*, 618-623, *supra* at note 214; U.S. Congressional Budget Office, *Research and Development in the Pharmaceutical Industry*, 21, *supra* at note 179.

³⁹⁰ *Drug Price Competition and Patent Term Restoration Act of 1984, Public Law 98-417*.

³⁹¹ U.S. Congressional Budget Office, *Research and Development in the Pharmaceutical Industry*, 16-17, *supra* at note 179.

³⁹² See Cahoy, *Medical Product Information Incentives and the Transparency Paradox*, 638, *supra* at note 183.

³⁹³ Food and Drug Administration, "FDA Public Health Advisory: Suspended Marketing of Tysabri (natalizumab)," FDA, <http://www.fda.gov/cder/drug/advisory/natalizumab.htm>

³⁹⁴ Food and Drug Administration, *FDA Approves Resumed Marketing of Tysabri Under a Special Distribution Program*, *supra* at note 278.

³⁹⁵ U.S. Government Accountability Office, *Improvement Needed in FDA's Postmarket Decision-Making and Oversight Process*, 2, footnote 6, *supra* at note 15.

the future landscape for prescription medical products, industry stakeholders have demanded a seat at the table. Recent efforts by industry to influence future methodologies, science, and infrastructure have been channeled through non-profit foundations and public-private partnerships. To address the FDA's new efforts, biopharmaceutical corporations have sought representation in the stalled Reagan-Udall Foundation created by the FDAAA³⁹⁶, as well as the Foundation for the National Institutes of Health's Observational Medical Outcomes Partnership, an organization intended to supplement the FDA's new postmarket activities.³⁹⁷ With respect to comparative effectiveness, the industry opposes these provisions of the stimulus bill and is lobbying the new Federal Coordinating Council for Comparative Effectiveness Research to sever any links to coverage decisions.³⁹⁸ Unlike the industry-heavy Observational Medical Outcomes Partnership or its partial influence on the Reagan-Udall Foundation, industry representatives do not have a seat on the Federal Coordinating Council.

Another indication of the industry's position on future innovation is the changing mix of prescription medical products being developed. The old biopharmaceutical business model of a "blockbuster drug," a drug developed for the widest possible use, is increasingly giving way to specialist medications which are typically administered by providers (e.g., oncology therapies).³⁹⁹ Signals that the FDA will require more extensive postmarket followup programs for cardiovascular and diabetes therapies explain part of this shift.⁴⁰⁰ Additionally, prescription medical products that have widespread utilization

³⁹⁶ Title VI: Reagan-Udall Foundation in *Food and Drug Administration Amendments Act of 2007*, Public Law 110-85, codified at 21 USC § 379dd.

³⁹⁷ Observational Medical Outcomes Partnership, "Observational Medical Outcomes Partnership: About Us," Foundation for the National Institutes of Health, <http://omop.fnih.org/?q=node/22> (accessed April 15, 2009).

³⁹⁸ Salant and Marcus, *Drugmakers Boost Lobbying to Police Drug Comparisons (Update1)*, *supra* at note 353. Robert Pear, "U.S. to Study Effectiveness of Treatments," *The New York Times*, sec. A, February 16, 2009.

³⁹⁹ Bethan Hughes, "2008 FDA Drug Approvals," *Nature Reviews Drug Discovery* 8, no. 2 (January 2009), 93-96; Bethan Hughes, "News Feature: 2008 in Reflection," *Nature Reviews Drug Discovery* 8, no. 1 (January 2009), 6... "Companies are increasingly reducing or halting their R&D in the once core area of cardiovascular disease."

⁴⁰⁰ U.S. Department of Health and Human Services, Food and Drug Administration and Center for Drug Evaluation and Research, "Guidance for Industry: Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention," FDA, <http://www.fda.gov/cder/guidance/7630dft.htm> (accessed April 18, 2009)... "Therapies that have not demonstrated a deleterious effect on cardiovascular outcome

patterns have been the source of the most significant postmarket failures. This should be unsurprising because larger and more heterogeneous real-world populations are likely to account for more variation in inadvertent and unwanted side effects. Finally, the blockbuster trend also runs counter to the emerging pharmacogenomics paradigm made possible by advances in genetics, which envisions certain products to be limited to certain users. If pharmacogenomics is to be the wave of the future, postmarket evidence management in both safety and comparative effectiveness will become more important to identify the subgroups of patients that could benefit most from using a particular prescription medical product.

5. Payors

Payors have been strong proponents of policies to develop better evidence for prescription medical products because it is in their interest to save money on unnecessary or ineffective treatments. Often, they have limited reimbursement policies for unproven therapies⁴⁰¹, which has put them at odds with other healthcare stakeholders. As a former CMS chief medical officer noted, "The increased adoption of the evidence-based medicine (EBM) framework without any reasonable way to accommodate promising technologies places payers between medical innovations and the patients and clinicians who want them."⁴⁰²

Many health plans negotiate this boundary with a pharmacy and therapeutic committee that considers the evidence regarding the relative effectiveness of different prescription medical products and recommends which ones should be reimbursed or given preferred status.⁴⁰³ For instance, fifteen states and two non-profit organizations work with the Drug Effectiveness Review Program, which synthesizes clinical

during extensive premarketing evaluation may need further post-approval assessment for their effects on long-term macrovascular disease."

⁴⁰¹ For example, see M. A. Hlatky, G. D. Sanders and D. K. Owens, "Evidence-Based Medicine and Policy: The Case of the Implantable Cardioverter Defibrillator," *Health Affairs* 24, no. 1 (Jan-Feb, 2005), 42-51. See also M. R. Gillick, "Medicare Coverage for Technological Innovations--Time for New Criteria?" *The New England Journal of Medicine* 350, no. 21 (May 20, 2004), 2199-2203; Garrison and others, *Using Real-World Data for Coverage and Payment Decisions: The ISPOR Real-World Data Task Force Report*, 326-335, *supra* at note 13.

⁴⁰² Tunis and Pearson, *Coverage Options for Promising Technologies: Medicare's 'Coverage with Evidence Development'*, 1220, *supra* at note 236.

⁴⁰³ U.S. Congressional Budget Office, *Research on the Comparative Effectiveness of Medical Treatments: Issues and Options for an Expanded Federal Role*, 8, *supra* at note 6.

information on drug classes, to inform their formulary decisions.⁴⁰⁴ In some cases, payors have formed their own research functions to assess emerging technologies, as in the Blue Cross Blue Shield Technology Evaluation Center.⁴⁰⁵ Wellpoint, United HealthCare, Kaiser Permanente and others have indicated that they have developed or will develop their own prescription medical product surveillance systems using their administrative claims databases.⁴⁰⁶ It is also likely that the more established databases will be seed data for public efforts to develop public health information infrastructure.

Other payors have used direct financial incentives to improve care such as Geisinger Health System's Proven Care model, which grants payment incentives to providers who use best practice care.⁴⁰⁷ Additionally, payors have fully supported the recent government interest in comparative effectiveness research, and are providing a powerful counter-lobby to the drug and device industry.⁴⁰⁸ These actions underscore a general willingness to support postmarket evidence development.

6. Other

Aside from the main stakeholders mentioned herein, a number of smaller stakeholders have an interest in future public health information infrastructure. First, the academic community is involved to the extent that much of the epidemiologic research that is conducted on behalf of public health agencies is contracted out to researchers. The primary players are the FDA- and AHRQ-managed Centers for Research and Education on Therapeutics (CERTs), the AHRQ's Evidence-based Practice Centers, and the FDA's longstanding contracts to use administrative data for epidemiology studies. New opportunities are already on the horizon for research advances in methodology, database management, decision analysis, and risk management. Second, information technology vendors - both electronic health record companies and algorithm/data-mining companies - will be affected by the outcome of future developments. These groups have already

⁴⁰⁴ P. J. Neumann, "Emerging Lessons from the Drug Effectiveness Review Project," *Health Affairs* 25, no. 4 (Jul-Aug, 2006), W262-71.

⁴⁰⁵ U.S. Congressional Budget Office, *Research on the Comparative Effectiveness of Medical Treatments: Issues and Options for an Expanded Federal Role*, 8, *supra* at note 6.

⁴⁰⁶ Vanessa Fuhrmans, "Insurers, FDA Team Up to Find Problem Drugs," *The Wall Street Journal*, sec. D, April 15, 2008.

⁴⁰⁷ L. M. Etheredge, "Medicare's Future: Cancer Care," *Health Affairs* 28, no. 1 (Jan-Feb, 2009), 156-157.

⁴⁰⁸ Salant and Marcus, *Drugmakers Boost Lobbying to Police Drug Comparisons (Update1)*, *supra* at note 353.

attended various planning meetings and have been working with the primary stakeholders to stay involved.⁴⁰⁹ Third, third-party think tanks and other non-profit organizations have taken on the role of neutral facilitators during policy discussions and public meetings. For example, the Brookings Institution is sponsoring a series of meetings with respect to the FDA's Sentinel Network and is acting as a convener on comparative effectiveness issues.⁴¹⁰ Other regular participants include the Robert Wood Johnson Foundation, the Markle Foundation/Connecting for Health.org, the eHealth Initiative Foundation, and the Institute for Safe Medical Practices.

B. Motivation to Change –Now is the Time

With most policy issues, there is a certain window of opportunity, during which stakeholders are most poised to enact changes. These windows occur for a number of reasons, but typically evolve because new technologies, policies, or shifts in political power change the landscape. New opportunities and the political will to act drive change. Often, they are the result of a "burning platform," described in business schools as either a natural or man-made urgency or crisis. Documented regulatory failures in the landmark IOM study on prescription medical product safety⁴¹¹ served as the crisis in postmarket evidence development and utilization. Congress's reform provisions in the FDAAA were clearly an order to act. While some regarded the changed landscape as a routine once every forty-years pendulum swing, other stakeholders saw a permanent and seismic shift in the way that postmarket data are regarded.⁴¹² As this section will describe, many

⁴⁰⁹ See various miscellaneous public comments in Food and Drug Administration, eHealth Initiative Foundation and Brookings Institute, *Sentinel Initiative: Structure, Function, and Scope*, 1-152, *supra* at note 357.

⁴¹⁰ Engelberg Center for Healthcare Reform, "Evidence-Based Health Care," Brookings Institution, <http://www.brookings.edu/health/Projects/evidence.aspx> (accessed April 16, 2009).

⁴¹¹ Institute of Medicine (IOM), *The Future of Drug Safety: Promoting and Protecting the Health of the Public*, 332, *supra* at note 15.

⁴¹² See commentary in McClellan, *Drug Safety Reform at the FDA--Pendulum Swing Or Systematic Improvement?*, 1700-1702, *supra* at note 178; and Johnson and Winslow, *Side Effect: Drug Makers Say FDA Safety Focus is Slowing New-Medicine Pipeline*, 1, *supra* at note 371... "Over at Schering-Plough, Mr. Hassan remains convinced there's been a paradigm shift, and he's been taking a hard look at medicines in the company's pipeline." See also Michael McCaughan, "JP Garnier's Farewell Address: The Lessons of Avandia (Part 1)," *The In Vivo Blog* (2008), <http://invivoblog.blogspot.com/2008/02/jp-garniers-farewell-address-lessons-of.html> (accessed April 18, 2009)...discussing the final words of an outgoing pharmaceutical executive: "Garnier's message: the safety-first regulatory climate of 2007 is not going away."

stakeholders jumped to take advantage of an opportunity to influence the future trajectory.

In clinical comparative effectiveness and cost effectiveness, there has not been a similar lightning rod. Rather, the unsustainable growth in healthcare expenditures coupled with the fear that valuable resources are being wasted on ineffective care is more of a slow, long simmering problem. The elephant in the room that delays decision-making is the specter of healthcare rationing. Bills calling for the creation and funding of a clinical comparative effectiveness center or agency have been circulating for more than five years.⁴¹³ It is the large increase in funding in the 2009 stimulus bill and the public testimony of incoming Obama Administration officials supporting comparative effectiveness⁴¹⁴ that have re-ignited efforts in this area.

It is no secret that comparative effectiveness proponents are taking advantage of existing policy windows to build infrastructure that have been opened up by Congress's actions on drug safety. The postmarket data desired for both purposes have considerable overlaps. The government stakeholders attending public planning meetings for the FDA's planned Sentinel Initiative are the same people that sit on the Federal Coordinating Council for Comparative Effectiveness Research.⁴¹⁵ In general, the implementation of new policies along with the promise of new technologies and funding have motivated stakeholders to get involved in efforts to fashion future public health information infrastructure development.

⁴¹³ See *Comparative Effectiveness Research Act of 2008 (S 3408)*, 110th, 2nd sess., *Congressional Record*, (July 31, 2008): 7908-7966 (accessed April 7, 2009); *Prescription Drug Comparative Effectiveness Act of 2006 (HR 5975)*, 109th, 2nd sess., *Congressional Record*, (July 28, 2006): 6230 (accessed April 7, 2009); *Prescription Drug Comparative Effectiveness Act of 2003 (HR 2356)*, 108th, 1st sess., *Congressional Record*, (July 28, 2003): 5042 (accessed April 7, 2009).

⁴¹⁴ Testimony of Kathleen Sebelius in U.S. Senate Committee on Health, Education, Labor, and Pensions, *Hearing to Examine the Nomination of Kathleen Sebelius to be Secretary of Health and Human Services*, 111th Cong., 1st sess., 2009... "So I think having the best possible research -- comparative research on alternative interventions to inform not only health-care providers across the country about what works and what's the most effective strategy but health consumers -- we're talking about informing consumers and having individuals learn more about their health outcomes, take more responsibility."

⁴¹⁵ See Food and Drug Administration, eHealth Initiative Foundation and Brookings Institute, *Sentinel Initiative: Structure, Function, and Scope*, 1-9, *supra* at note 357; and compare with Department of Health and Human Services, *Federal Coordinating Council for Comparative Effectiveness Research Membership*, *supra* at note 346.

1. New Internet Technologies Enable Public Involvement

"This changing role [of evidence] will require healthcare providers and patients to adopt a culture that supports the generation and application of evidence."⁴¹⁶

The Internet has revolutionized the way that Americans can learn about the available evidence on prescription medical products. Aided by the use of new information communication technologies such as social networks and non-traditional journalism sources such as weblogs, the general public is becoming more active in learning about their care.⁴¹⁷ Clinical trial results⁴¹⁸, transcripts of advisory committee meetings⁴¹⁹, formal FDA approval packages⁴²⁰, journal articles indexed by the National Library of Medicine⁴²¹, and even portions of the adverse event reporting system⁴²² are available online. Recently, the FDA has announced its intention to partner with WebMD.com to communicate emerging information.⁴²³ Also, the Federal Coordinating Council for Comparative Effectiveness Research is holding three virtual meeting sessions to hear public comment on spending the nearly \$700 million dollars that is still unspent and allocated to comparative effectiveness research.⁴²⁴ In sum, information technologies connect stakeholders in ways that might have been unimaginable years ago.

⁴¹⁶ Institute of Medicine (IOM), *Evidence-Based Medicine and the Changing Nature of Health Care: 2007 IOM Annual Meeting Summary*, 46, *supra* at note 7.

⁴¹⁷ Food and Drug Administration, "FDA Teams with WebMD for New Online Consumer Health Information," FDA, <http://www.fda.gov/bbs/topics/NEWS/2008/NEW01918.html> (accessed April 14, 2009)... "Researchers found that 32 percent of American consumers—70 million adults—conducted online health searches in 2007, compared with 16 percent in 2001... More than half of those surveyed said the information changed their overall approach to maintaining their health. Four in five said the information helped them better understand how to treat an illness or condition."

⁴¹⁸ Clinicaltrials.gov, National Library of Medicine; National Institutes of Health; Department of Health and Human Services, <http://clinicaltrials.gov/> (accessed April 14, 2009).

⁴¹⁹ Food and Drug Administration, "Advisory Committees," FDA, <http://www.fda.gov/oc/advisory/default.htm> (accessed April 14, 2009).

⁴²⁰ Center for Drug Evaluation and Research and Food and Drug Administration, "Drugs@FDA: FDA Approved Drug Products," FDA, <http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA/> (accessed April 14, 2009).

⁴²¹ PubMed.gov, National Library of Medicine; National Institutes of Health, <http://www.ncbi.nlm.nih.gov/pubmed/> (accessed April 14, 2009).

⁴²² Center for Drug Evaluation and Research and Food and Drug Administration, "The Adverse Event Reporting System: Latest Quarterly Data Files," FDA, <http://www.fda.gov/cder/aers/extract.htm> (accessed April 14, 2009).

⁴²³ Food and Drug Administration, *FDA Teams with WebMD for New Online Consumer Health Information*, *supra* at note 417... "[Consumers] learn how to report problems involving the safety of these products directly to the FDA. In addition, WebMD will bring the FDA public health alerts to all WebMD registered users and site visitors that request them."

⁴²⁴ Department of Health and Human Services, "Comparative Effectiveness Research Funding," DHHS, <http://www.hhs.gov/recovery/programs/ceer/index.html> (accessed April 23, 2009).

More importantly, the information age has transformed the capacity of citizens to monitor the actions of the stakeholders - government agencies, biopharmaceutical companies, insurance companies/health plans, and even their providers – who most impact the medical products that increasingly affect their lives. Citizens can provide electronic notice and comment to government agencies, can virtually attend public meetings, can quickly and easily communicate with their Congressional representatives, and can often interact online with their medical records, providers, and pharmacy benefit managers. In fact, many of the patient registries utilized by medical associations and sponsors are completely administered online.⁴²⁵ Information communication technologies give the public the opportunity to influence future public health information infrastructure and to directly contribute postmarket data if desired. This access empowers patients to demand better evidence on safety, clinical effectiveness, and cost effectiveness; to demand transparency and accountability from stakeholders that hold sway over their care; and to fully participate in the policy process and in their healthcare delivery.

2. New Technology Investments Signal Opportunities

From a supply-side perspective, network technology and distributed database management also enable new potential approaches to postmarket evidence collection. Congress's mandate to create an active postmarket risk identification and analysis system reflects its belief in this technology as the way forward. Active surveillance began to gain momentum after the Vioxx™ (rofecoxib) scandal when the IOM recommended "systematically implement[ing] statistical-surveillance methods on a regular and routine basis for the automated generation of new safety signals" and "develop[ing] and implement[ing] active surveillance of specific drugs and diseases as needed in a variety of settings."⁴²⁶ Detecting a Vioxx™-like (rofecoxib) issue - the increased frequency of a common adverse reaction (e.g., heart attacks) in a population with a significant underlying disease burden – is a particularly challenging epidemiologic problem that requires significant access to temporal data, an unlikely probability without a robust

⁴²⁵ See, for example, Biogen Idec, "Tysabri (Natalizumab): Touch™ Prescribing Program," Biogen Idec, <http://www.tysabri.com/tysbProject/tysb.portal> (accessed May 3, 2009).

⁴²⁶ Institute of Medicine (IOM), *The Future of Drug Safety: Promoting and Protecting the Health of the Public*, 7, *supra* at note 15.

public health information infrastructure. This "greenfield" presents new opportunities for data owners, information technology vendors, computer scientists, statistical software developers, researchers and many more. The complicated nature of the task at hand – connecting disparate patient data across time and space while respecting privacy, security, proprietary, legal and other constraints - necessitates the involvement of a wide variety of problem solvers and entrepreneurs. In short, it is an attractive new platform to invest in technology, provide solutions to unsolved problems, and generally to move in innovative new directions.

3. New Investments in Human Resources are Imminent

The development of new infrastructure not only provides new opportunities for technology, software, and hardware, but also can enhance current fields of research and develop new fields as appropriate. The combination of hard problems, the need for new solutions, and a sustainable line of funding to solve those problems is an ample opportunity for academics, scientists, and researchers to get involved. In order to perform postmarket safety or comparative effectiveness assessments using the next public health information infrastructure, epidemiologists, statisticians, complex system modelers, and other researchers will be charged with developing reliable methodologies to analyze observational data. Methodological developments in pharmacoepidemiology and comparative effectiveness have a long way to catch up to the methods developed for randomized clinical trials.⁴²⁷ In 2007, the AHRQ commissioned an entire issue of *Medical Care* to highlight the important challenges that must be solved.⁴²⁸ The IOM's Evidence Based Roundtable and Learning Healthcare Program also have lent support.⁴²⁹

⁴²⁷ Avorn, *In Defense of Pharmacoepidemiology--Embracing the Yin and Yang of Drug Research*, 2219-20, *supra* at note 107; S. Schneeweiss, "Developments in Post-Marketing Comparative Effectiveness Research," *Clinical Pharmacology and Therapeutics* 82, no. 2 (Aug, 2007), 143-156.

⁴²⁸ Agency for Healthcare Research and Quality, "Emerging Methods in Comparative Effectiveness and Safety - *Medical Care* Supplement," AHRQ, <http://effectivehealthcare.ahrq.gov/healthInfo.cfm?infotype=nr&ProcessID=32> (accessed January 10, 2009).

⁴²⁹ Institute of Medicine (IOM), *Learning Healthcare System Concepts v2008: Annual Report*, 29-34, *supra* at note 57... "The kinds of 'safe harbor' opportunities that exist in various fields for developing and testing innovative methodologies for addressing complex problems are rarely found in clinical research. Initiative is needed for the research community to challenge and assess its approaches—a sort of meta-experimental strategy—including those related to analyzing large data sets, in order to learn about the purposes best served by different approaches."

In the government sector, human resource development opportunities have increased. The FDA has new funding resources for staffing⁴³⁰ and has already issued a handful of short-term research contracts.⁴³¹ Adding to the momentum to develop new scientific human resources are actions by the FDA announcing a new fellowship program to bring more scientists and academics onboard and to lay the foundation for a future training pipeline.⁴³² On the comparative effectiveness front, stimulus funding must be spent imminently.⁴³³ It is unclear how appropriations to the AHRQ and the DHHS will be used to further comparative effectiveness research, but it is likely that much of the funding will be used to stimulate extramural research. The NIH has already begun its efforts to distribute \$400 million in two-year stimulus grants by the end of this year.⁴³⁴ In general, a note of caution remains because of the one-off nature of this particular source of funding. Investment in permanent human resource infrastructure typically requires a more stable and sustainable base of government appropriations. Nonetheless, if the Administration is seriously committed to comparative effectiveness research, follow-on funding to supplement an existing government agency or to create an agency dedicated to comparative effectiveness research is possible.

The government's investment in future public health information infrastructure had knock-on effects, spurring private investment in research designed to influence its evolution. Via the FDAAA, Congress also created the Reagan-Udall Foundation, a private nonprofit corporation with the purpose of advancing the mission of the FDA.⁴³⁵ The Reagan-Udall Foundation was patterned after the Foundation for the NIH (fNIH),

⁴³⁰ Associated Press, "FDA Beefs Up Workforce with 1300 New Staffers," *The San Francisco Chronicle*, sec. C, September 12, 2008. See also Hughes, *2008 FDA Drug Approvals*, 96, *supra* at note 399...reporting that nearly 400 new staff were added to the Center for Drug Evaluation and Review in FY2008.

⁴³¹ Food and Drug Administration, eHealth Initiative Foundation and Brookings Institute, *Sentinel Initiative: Structure, Function, and Scope*, 17-18, *supra* at note 357. These contracts have focused on evaluation of data sources, data models, methods, and engagement.

⁴³² Food and Drug Administration, "FDA Launches Fellowship Program to Develop Pipeline of Scientists, Other Professionals," FDA, <http://www.fda.gov/bbs/topics/NEWS/2008/NEW01861.html> (accessed April 14, 2009)... "The FDA is a science-based regulatory agency, and to fulfill our mission over the coming decade we will need to recruit thousands of highly skilled scientists and others with specialized and relevant expertise," said Frank M. Torti, M.D., M.P.H., principal deputy commissioner and chief scientist."

⁴³³ Title VIII: Departments of Labor, Health and Human Services, and Education, and Related Agencies in *American Recovery and Reinvestment Act of 2009, Public Law 111-5*.

⁴³⁴ U.S. Department of Health and Human Services and Office of Extramural Research at National Institutes of Health, *NIH Challenge Grants in Health and Science Research (RC1)*, *supra* at note 47.

⁴³⁵ Title VI: Reagan-Udall Foundation in *Food and Drug Administration Amendments Act of 2007, Public Law 110-85*, codified at 21 USC § 379dd.

which was chartered by Congress in 1990.⁴³⁶ These foundations are public-private partnerships permitted to solicit and accept donations from private entities⁴³⁷; they are envisioned as a mechanism to perform innovative research that might be too expensive and too high-risk for broad public funding.⁴³⁸ Mark McClellan, former head of the CMS and the FDA and current chairman of the Reagan-Udall Foundation, has hinted that the FDA's core funding is insufficient to cover the costs of a future infrastructure (including initial research on methods and analyses).⁴³⁹ Speculation that the FDA's infrastructure development would be delegated to the Reagan-Udall Foundation led the chair of the FDA appropriations subcommittee to suspend appropriating previously authorized public funds until policies could be established to preclude undue industry influence on its actions.⁴⁴⁰ Consequently, the Reagan-Udall Foundation has been raising private funds for its operations.

Once it was clear that the Reagan-Udall Foundation would be temporarily unavailable as a funding mechanism, industry stakeholders partnered with the FDA and the Foundation for the NIH to form the Observational Medical Outcomes Partnership (OMOP) – "a two-year initiative to research methods that are feasible and useful to analyze existing healthcare databases to identify and evaluate safety and benefit issues of drugs already on the market."⁴⁴¹ The OMOP has already hired staff, created various

⁴³⁶ Rosa DeLauro, "Strengthening the FDA; to Reform, End Political Interference," *The Washington Times*, Editorial, March 5, 2008.

⁴³⁷ Title VI: Reagan-Udall Foundation in *Food and Drug Administration Amendments Act of 2007*, Public Law 110-85, codified at 21 USC § 379dd(i).

⁴³⁸ M. McClellan, "An Audience with Mark McClellan," *Nature Reviews Drug Discovery* 8, no. 2 (February, 2009), 102-102, <http://dx.doi.org/10.1038/nrd2816>... "There are private foundations and non-profit groups that are interested in seeing the big gaps in product development addressed, particularly in personalized medicine and post-market drug safety, and could provide another source of funding."

⁴³⁹ Remarks of Mark McClellan in Food and Drug Administration, eHealth Initiative Foundation and Brookings Institute, *Sentinel Initiative: Structure, Function, and Scope*, 139, *supra* at note 357.

⁴⁴⁰ See R. L. DeLauro, "Calls on FDA to Cease Activities Creating Reagan-Udall Foundation," Office of Congresswoman Rosa L. DeLauro, http://delaurow.house.gov/text_release.cfm?id=839 (accessed April 17, 2009)... "Although Congress intended the Reagan-Udall Foundation to be a public-private partnership, unless carefully structured it will be a non-profit group controlled primarily by private industries that the FDA regulates." See also DeLauro, *Strengthening the FDA; to Reform, End Political Interference*, *supra* at note 436.

⁴⁴¹ Observational Medical Outcomes Partnership, *Observational Medical Outcomes Partnership: About Us*, *supra* at note 397. See also Observational Medical Outcomes Partnership, "Charter for the Observational Medical Outcomes Partnership," Foundation for the National Institutes of Health, <http://omop.fnih.org/sites/default/files/OMOP%20Charter%20February%202009.pdf> (accessed April 15, 2009).

oversight boards, and begun a research application process.⁴⁴² These efforts are clearly aimed to influence the development of future public health information infrastructure and are the industry's means of asserting its stake in the matter. However, the funding also primes the pump of human resources infrastructure as growth in this area will compliment the technical infrastructure being built.

4. New Legal/Regulatory Schemes Even the Playing Field

Struck by the American public's dependence on a substantially underfunded, overburdened, internally divided, and generally weak FDA⁴⁴³, Congress changed the balance of regulatory power in the postmarket and emboldened the FDA to intervene more assertively to protect the American people.⁴⁴⁴ Prior to its passage, the FDA postmarket divisions did not have the funding or influence to act on the data they collected to inform the safe and effective use of prescription medical products.⁴⁴⁵ A cultural divide had persisted between the premarket and postmarket divisions culminating in a public shaming of the agency. Additionally, the FDA had little enforcement power other than the mandatory withdrawal of a prescription medical product, an authority it was reluctant to use because the balance of interests often favored more stringent control shy of outright removal.⁴⁴⁶

The shaping of a future public health information infrastructure gives the FDA a substantial opportunity to remedy its deficiencies and to reclaim its image with the American public. Symbolically, the legislation also sent a signal to industry that Congress has elevated the FDA's abilities in order to keep it on even footing with powerful industry

⁴⁴² Observational Medical Outcomes Partnership, "Observational Medical Outcomes Partnership: Requests for Application," Foundation for the National Institutes of Health, <http://omop.fnih.org/?q=node/68> (accessed April 15, 2009).

⁴⁴³ Food and Drug Administration, *FDA Science and Mission at Risk: Report of the Subcommittee on Science and Technology*, *supra* at note 171; Harris, *F.D.A. Panel Votes to Keep Diabetes Drug on Market*, *supra* at note 339.

⁴⁴⁴ Title IX: Enhanced Authorities Regarding Postmarket Safety of Drugs in *Food and Drug Administration Amendments Act of 2007, Public Law 110-85*, codified in various sections of 21 U.S.C. § 331, 334, 352, 353, 355, 360, 381.

⁴⁴⁵ Testimony of David Graham in U.S. Senate Committee on Finance, *FDA, Merck, and Vioxx: Putting Patient Safety First?*, *supra* at note 23... "At the same time, the Office of Drug Safety has no regulatory power and must first convince the New Drug Reviewing Division that a problem exists before anything beneficial can be done to help the public."

⁴⁴⁶ Institute of Medicine (IOM), *The Future of Drug Safety: Promoting and Protecting the Health of the Public*, 58, *supra* at note 15.

interests. The picture is not perfect; conflicts of interest related to user fee applications still plague the agency and new revelations of whistleblower suppression continue to damage it.⁴⁴⁷ Still, the FDA's new powers of enforcement serve as political teeth to strength the FDA's hand in taking appropriate risk management and communication actions when postmarket evidence dictates. In general, both the industry and the FDA benefit from restoring the FDA's reputation. Biopharmaceutical companies know that the perception of a weak FDA does not help them sell their products or convince the public of their safety and efficacy.⁴⁴⁸ The FDA's public demonstration of its intention to be more responsive in the postmarket has taken shape in its overhaul of risk communications, its increased use of risk evaluation and management strategies (REMS) attached to new product approvals, its first FDA-ordered labeling changes, and the signing of a Memorandum of Understanding between the premarket and postmarket divisions within the FDA to give the postmarket divisions more equal standing. These are signals, sent to all stakeholders, to mark the FDA's present and future willingness to change its postmarket behaviors and to return to a state of trust and credibility.

In the regulatory realm, one of the FDA's immediate actions was to begin a program of "early communications" to warn patients and providers of emerging potential postmarket risks submitted to the adverse event reporting system. These early communications are press releases of potential safety issues, which carry the disclaimer:

"This information reflects FDA's current analysis of available data concerning these drugs. Posting this information does not mean that FDA has concluded there is a causal relationship between the drug products and the emerging safety issue. Nor does it mean that FDA is advising health care professionals to discontinue prescribing these products. FDA is considering, but has not reached a conclusion about whether this information warrants any regulatory action. FDA intends to update this document when additional information or analyses become available."⁴⁴⁹

These press releases have been summarized quarterly, per the FDAAA, on the FDA website as "Potential Signals of Serious Risks/New Safety Information Identified from

⁴⁴⁷ See U.S. Senate Committee on Finance and C. Grassley, "Letter to President Obama from FDA Physicians, scientists," U.S. Senate Committee on Finance, <http://finance.senate.gov/press/Gpress/2009/prg040209a.pdf> (accessed May 1, 2009).

⁴⁴⁸ Wood, *Playing "Kick the FDA"--Risk-Free to Players but Hazardous to Public Health*, 1774-1775, *supra* at note 169.

⁴⁴⁹ Center for Drug Evaluation and Research and Food and Drug Administration, "Early Communication about on Ongoing Safety Review: Omeprazole (Prilosec) and Esomeprazole (Nexium)," FDA, http://www.fda.gov/cder/drug/early_comm/omeprazole_esomeprazole.htm (accessed April 14, 2009).

the Adverse Event Reporting System."⁴⁵⁰ In terms of benefit-risk management, the FDA has lowered its threshold for public reporting such that an unconfirmed potential association is announced prior to establishing either correlation or causality. Thus, depending on its judgment of the seriousness of the risk, the FDA is relying to the public the status of its adverse event reporting system and its intentions to act on a suspected drug-outcome association. This change in policy signals a shift toward use of the precautionary principle; it is valuable if used judiciously to invite providers and patients to engage in thoughtful examination of their use of prescription medical products.

Some have protested these actions, stating that the use of early warnings has caused people to abruptly discontinue necessary medications.⁴⁵¹ This argument is unpersuasive and insulting to the American public. Any situation in which a patient makes a unilateral decision to discontinue a medication is undesirable. The root of that problem is the patient's relationship with his or her provider, not the availability of new information. False positives are a legitimate concern, but it is because of the time, effort, and opportunity costs that are spent pursuing wrong directions. The FDA's new tools empower patients and providers to be more aware of the present state of knowledge and to make logical decisions based on preferences and needs. When substitutes are available for particular therapeutics, stakeholders may prefer to switch to medications without potential signals of serious risks. Additionally, it is possible that patients may prefer to avoid medication until the risks are better understood. Ultimately, the goal of such programs is to engage the public and their providers more actively in choosing the best care depending on their needs and values while participating in public processes to develop better data. Stakeholders have a greater willingness to participate in any system when they are strongly invested in the need to close gaps in knowledge.

Risk Management and Evaluation Strategies (REMS) have served both patients and industry well as a third way to manage risk while simultaneously rebuilding trust. That is, potential adverse events from high-risk products can be reasonably mitigated

⁴⁵⁰ Center for Drug Evaluation and Research and Food and Drug Administration, "Potential Signals of Serious Risks/New Safety Information Identified from the Adverse Event Reporting Systems (AERS)," FDA, http://www.fda.gov/cder/aers/potential_signals/default.htm (accessed April 14, 2009). The legislative requirements can be found in Section 921: Adverse Drug Reaction Reports and Postmarket Safety in *Food and Drug Administration Amendments Act of 2007, Public Law 110-85*, codified at 21 U.S.C. § 355(k)(5).

⁴⁵¹ Shirley S. Wang, "Drug-Safety Data: Too Much Information?" *The Wall Street Journal*, sec. D, December 9, 2008.

through the use of tailored restrictions that allow a company to receive a return on their investment rather than scrap a product. REMS are the third generation of restricted distribution programs that began with Subpart H approvals⁴⁵² and RiskMAPs.⁴⁵³ While the FDA had limited prior discretion to use such techniques, Congress expanded this discretion, but formalized it by requiring assessment and other communication procedures when REMS are utilized.⁴⁵⁴ In some cases, the new postmarket mechanisms enacted by Congress via the FDAAA have saved the patent life of prescription medical products. In 2008, three new products were approved with REMS that might otherwise have never made it to market.⁴⁵⁵

Cases like Tysabri™ (natalizumab) and thalidomide (e.g., carefully managed drugs that have proven beneficial to patients and profitable to companies) help make the case that careful utilization of a REMS is a business solution (and possible strategic advantage) to the challenges of marketing high-risk medications. Such a program prevents the loss of a product (via a non-approval or withdrawal) entirely. The short-term cost of a REMS is that it limits rapid rollout of medications until more experience is gained with them in the postmarket. However, these short-term costs are more than recovered by avoiding the costs associated with potentially ill-informed, large-scale utilization of products with uncertain risk profiles in populations not well-suited to manage the uncertainty. The strategy of incremental rollout has served oncology markets (note: high-toxicity) well by building early confidence in, and experience with, the product. Postmarket monitoring develops a pattern of risks and benefits that allows all stakeholders to adapt more rapidly and effectively to new information. Thus, the use of REMS as a tool in conjunction with a new public health information infrastructure is a

⁴⁵² Food and Drug Administration and Department of Health and Human Services, *New Drug, Antibiotic, and Biological Drug Product Regulations; Accelerated Approval*, 58942-58960, *supra* at note 128.

⁴⁵³ U.S. Department of Health and Human Services and others, "Guidance for Industry: Develop and Use of Risk Minimization Action Plans," FDA, <http://www.fda.gov/cder/guidance/6358fnl.htm> (accessed April 18, 2009).

⁴⁵⁴ Risk Evaluation and Mitigation Strategies in *Food and Drug Administration Amendments Act of 2007, Public Law 110-85*, codified at 21 U.S.C. § 355-1.

⁴⁵⁵ Hughes, *2008 FDA Drug Approvals*, 93-96, *supra* at note 399. For more commentary, see Bridget Silverman, "REMS to the Rescue: Why FDA's Drug Safety Tools may Mean More Approvals this Year," *The in Vivo Blog* (2008), <http://invivoblog.blogspot.com/2008/07/rem-s-to-rescue-why-fdas-drug-safety.html> (accessed April 18, 2009)... "in [the three] case[s] the sponsor has been thrilled to have a product to market at all."

vital opportunity for the FDA and the biopharmaceutical industry to rebuild trust among patients and providers.

The FDA has made several smaller attempts to show renewed responsiveness to postmarket data. In 2008, the FDA began piloting a program of routine postmarket review of new molecular entities based on an IOM recommendation.⁴⁵⁶ The program was patterned after the European Medicines Agency's 2005 decision to allow for "provisional" or "conditional" approval of prescription medical products after five years of marketing.⁴⁵⁷ While the FDA has made no direct connection between its review of the postmarket profile of a medical product and that profile's effect on future regulatory action, the FDA is again demonstrating that it is willing to do more in the postmarket. Another example is the FDA's first use of a mandatory labeling order when negotiations with the sponsor failed.⁴⁵⁸ In a final demonstration of the FDA's willingness to change its behaviors, a memorandum of agreement was signed between the postmarket and premarket divisions granting them "equal rights" in July 2008.⁴⁵⁹ Such a move does much to assuage public fears that the FDA is dominated by premarket concerns and to give providers and the public a reason to take the FDA seriously as they pursue future policy efforts in the postmarket.

It is important to note that these new legal and regulatory tools largely address shortcomings in the second issue outlined in chapter one: the ineffective benefit-risk management of emergent information that has been generated through traditional postmarket mechanisms like spontaneous reporting. Through public demonstrations of its

⁴⁵⁶ Food and Drug Administration, "Post-Marketing Safety Evaluation of New Molecular Entities (NMEs): Progress Report," FDA, http://www.fda.gov/cder/drug/postmarketing_safety/default.htm (accessed May 2, 2009). The IOM recommended, "FDA evaluate all new data on new molecular entities no later than 5 years after approval." See Institute of Medicine (IOM), *The Future of Drug Safety: Promoting and Protecting the Health of the Public*, 173, *supra* at note 15.

⁴⁵⁷ *ibid.*

⁴⁵⁸ Center for Drug Evaluation and Research and Food and Drug Administration, "Complete Response and Safety Labeling Change Order to Amgen, Incorporated," FDA, <http://www.fda.gov/cder/drug/infopage/RHE/aranesp/signed.pdf> (accessed April 14, 2009). The FDA took issue over two points, one of which was the sponsor failing to restrict the use of the products strictly to terminal cancer patients undergoing chemotherapy.

⁴⁵⁹ Center for Drug Evaluation and Research and Food and Drug Administration, "Memorandum of Agreement between the Office of New Drugs and the Office of Surveillance and Epidemiology in the Center for Drug Evaluation and Research," FDA, http://www.fda.gov/cder/drug/DrugSafety/OSE_OND_MOA.pdf (accessed May 2, 2009)... "Under this agreement, OND and OSE have equal responsibility for the resolution of significant safety issues affecting drug products and determining appropriate regulatory action."

intent to change, the FDA has shown a new willingness and capacity to address postmarket issues. Its efforts generate confidence that it will be able to cope with the significant changes ahead.

V. Policy Goals for a New Public Health Information Infrastructure

First, this chapter covers the broad needs of a future public health information infrastructure: 1) to enable early warning systems for emergent safety issues; 2) to systematically approach comparative clinical effectiveness from both a population-based and a subgroup-based perspective; and 3) to establish mechanisms to evaluate the long-term effectiveness of prescription medical products in measures that matter to patients such as quality of life, morbidity, and mortality. Next, specific types of policy goals are examined with regard to the legal/regulatory, technological, scientific, organizational, social, and private sector changes necessary to make these goals feasible.

A. *Broad Needs of a Public Health Information Infrastructure*

1. Safety Concerns

The most significant and newsworthy issue of healthcare delivered in an environment of incomplete and imperfect information on the benefits and risks of prescription medical products is the potential for harm caused by adverse drug experiences (ADEs). ADEs can be traced to a multitude of causes and can range from the uncomfortable (e.g., a headache, nausea) to the serious, life-threatening, and fatal. Numerous studies have shown that ADEs cause significant personal and societal costs to the entire health care system. Budnitz et al. estimated that more than 700,000 patients were treated in emergency departments annually for ADEs in 2004 and 2005, a number that underestimates the total burden of ADEs because it does not include in-hospital events or more minor events suffered by outpatients.⁴⁶⁰ Classen et al. found that the human cost to a patient of suffering an in-hospital ADE was associated with a significantly prolonged length of stay, and an almost 2-fold increased risk of death.⁴⁶¹ An oft-cited and older meta-analysis showed that adverse drug reactions (excluding medication errors) were somewhere between the fourth and sixth leading cause of death

⁴⁶⁰ D. S. Budnitz and others, "National Surveillance of Emergency Department Visits for Outpatient Adverse Drug Events," *Journal of the American Medical Association* 296, no. 15 (Oct 18, 2006), 1858-1866.

⁴⁶¹ D. C. Classen and others, "Adverse Drug Events in Hospitalized Patients. Excess Length of Stay, Extra Costs, and Attributable Mortality," *Journal of the American Medical Association* 277, no. 4 (Jan 22-29, 1997), 301-306.

in the United States in 1994.⁴⁶² In terms of private financial losses, Bates et al. showed that preventable ADEs cost a 700-bed tertiary teaching hospital 2.8 million dollars in one year.⁴⁶³ In summary, personal harms to patients from ADEs can include pain and suffering from injuries, lost productivity, and avoidable additional health care costs. Because an increasing burden of healthcare costs is borne by taxpayers, unnecessary healthcare is also a social harm. Other social losses from ADEs include unnecessary private causes of action and diverted R&D expenditures, which are redirected into "damage control" when the general public learns latently of potentially harmful effects from prescription medical products.

2. Lack of Comparative Clinical Effectiveness Information

Without a trusted, evidence-based public health infrastructure on the comparative risks and benefits of various therapies, there are harms in the inability to distinguish the most effective medical products (or non-medication therapy) when multiple therapeutic options are present (i.e., choosing the most benefit with the least risk and cost). Because most therapeutics on the market are tested against placebos in order to show efficacy, there is little evidence of how these therapeutics perform against each other when many choices are available to treat a condition.⁴⁶⁴ Additionally, patients and providers tend to opt for the newest treatments available without substantial evidence of an improved benefit-risk profile, at a considerably higher cost.⁴⁶⁵ The ALLHAT trial, for example, was initiated because 50 to 60 million Americans are prescribed anti-hypertensive medical products to reduce morbidity and mortality, and yet the evidence about their relative risks and benefits was poor.⁴⁶⁶ Little guidance existed to aid providers and patients in choosing

⁴⁶² J. Lazarou, B. H. Pomeranz and P. N. Corey, "Incidence of Adverse Drug Reactions in Hospitalized Patients: A Meta-Analysis of Prospective Studies," *Journal of the American Medical Association* 279, no. 15 (Apr 15, 1998), 1200-1205.

⁴⁶³ D. W. Bates and others, "The Costs of Adverse Drug Events in Hospitalized Patients. Adverse Drug Events Prevention Study Group," *Journal of the American Medical Association* 277, no. 4 (Jan 22-29, 1997), 307-311.

⁴⁶⁴ Schneeweiss, *Developments in Post-Marketing Comparative Effectiveness Research*, 143-156, *supra* at 427.

⁴⁶⁵ U.S. Congressional Budget Office, *Research on the Comparative Effectiveness of Medical Treatments: Issues and Options for an Expanded Federal Role*, 1, *supra* at note 6.

⁴⁶⁶ ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, *Major Outcomes in High-Risk Hypertensive Patients Randomized to Angiotensin-Converting Enzyme Inhibitor Or Calcium Channel Blocker Vs Diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial*

among the five classes of therapeutics available. The trial results showed no improvement in outcomes for use of the newer and more expensive anti-hypertensive therapies; that is, the most effective first-course therapy was found to be the oldest and least expensive option.⁴⁶⁷ Sub-group studies of African-Americans, who bear a significant burden in hypertension, also showed no comparable outcome differences among the newest classes of anti-hypertensives.⁴⁶⁸

While there were not substantially different safety risks for the different classes, there were substantially different costs, which may affect the quality of life for many patients (particularly those on fixed incomes). ALLHAT, and trials like it, can reduce unnecessary social and personal healthcare costs by demonstrating the risks and benefits relative to substitutes. A frequent misconception of and fear about comparative effectiveness research assumes that it will privilege one population-level "answer" or therapy at the expense of alternatives.⁴⁶⁹ Such a monolithic perspective ignores the point of comparative effectiveness research: to establish better evidence on all the available therapies in comparison with an eye to practical endpoints that matter to patients and providers (i.e. morbidity, mortality, and quality of life). Successful research efforts must take great care in research design to consider subgroup cohorts since the most effective *collective* therapy may not be the most *effective subgroup therapy* due to natural variation among patient populations.

3. Opportunity Cost associated with Ineffective or Under-effective Therapies

In general, there has been little public recognition of the importance of identifying ineffective medications that may not cause significant or serious harm but that are expensive and/or provide few long-term benefits (e.g., small incremental decreases in

(*ALLHAT*), 2981-2997, *supra* at note 188; L. J. Appel, "The Verdict from ALLHAT--Thiazide Diuretics are the Preferred Initial Therapy for Hypertension," *Journal of the American Medical Association* 288, no. 23 (Dec 18, 2002), 3039-3042.

⁴⁶⁷ *ibid.*

⁴⁶⁸ A. L. Taylor and J. T. Wright Jr, "Should Ethnicity Serve as the Basis for Clinical Trial Design? Importance of race/ethnicity in Clinical Trials: Lessons from the African-American Heart Failure Trial (A-HeFT), the African-American Study of Kidney Disease and Hypertension (AASK), and the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)," *Circulation* 112, no. 23 (Dec 6, 2005), 3654-60; discussion 3666.

⁴⁶⁹ Pear, *U.S. to Study Effectiveness of Treatments*, *supra* at note 398, reporting that the Congressional Black Caucus said, "We are concerned that comparative effectiveness research will be based on broad population averages that ignore the differences between patients."

blood pressure or cholesterol using multiple medications without improvement in morbidity or mortality).⁴⁷⁰ Patients may be taking these medications instead of those with proven benefits, and thus pay an opportunity cost by forgoing other therapies. Harms may also occur when patients accept higher risks of side effects or increased costs because of the clinical promise of higher benefits. These higher benefits are often unproven in the initial premarket clinical trials because efficacy is shown via the use of surrogate or proxy endpoints. Surrogate endpoints, such as a reduction in blood pressure, are presumed to be linked to primary endpoints (i.e. improved morbidity or mortality) based on biological analyses and sometimes, animal studies. However, these presumed connections often go untested for years due to the required length and size of long-term clinical trials to test the primary endpoints.

The use of surrogate endpoints first began in the AIDS crisis when CD4 counts were used as a surrogate for mortality. Later trials only showed a weak correlation with the predicted clinical outcomes.⁴⁷¹ Most recently, two effectiveness trials related to Vytorin™ (ezetimibe) showed no improvement in long-term outcomes when compared to a generic statin.⁴⁷² Yet, Vytorin™ (ezetimibe) is nearly twice as expensive and has garnered a large market share since its launch.⁴⁷³ Vytorin™ (ezetimibe) was approved under a surrogate endpoint - a change in LDL cholesterol – under the assumption that continual reductions in cholesterol (beyond a regular statin or cholesterol-lowering medication) would produce long-term morbidity and mortality benefits.⁴⁷⁴ Surrogate end points are common in drug approvals for conditions that are known for cardiovascular risk factors (e.g., obesity, hypertension, hypercholesterolemia, and diabetes mellitus)

⁴⁷⁰ Pollack, *A Big Blood Pressure Study, and its Minimal Impact on Drug Use*, *supra* at note 68; Berenson, *For Widely Used Drug, Question of Usefulness is Still Linger*, *supra* at note 20.

⁴⁷¹ S. R. Shulman and J. S. Brown, "The Food and Drug Administration's Early Access and Fast-Track Approval Initiatives: How have they Worked?" *Food and Drug Law Journal* 50 (1995), 518.

⁴⁷² J. J. Kastelein and others, "Simvastatin with Or without Ezetimibe in Familial Hypercholesterolemia," *The New England Journal of Medicine* 358, no. 14 (Apr 3, 2008), 1431-1443; B. M. Psaty and T. Lumley, "Surrogate End Points and FDA Approval: A Tale of 2 Lipid-Altering Drugs," *Journal of the American Medical Association* 299, no. 12 (Mar 26, 2008), 1474-1476; A. B. Rossebo and others, "Intensive Lipid Lowering with Simvastatin and Ezetimibe in Aortic Stenosis," *The New England Journal of Medicine* 359, no. 13 (Sep 25, 2008), 1343-1356.

⁴⁷³ U.S. Senate Committee on Finance and Grassley, *Memorandum to Reporters and Editors on the Vytorin Study*, *supra* at note 20.

⁴⁷⁴ Krumholz and Lee, *Redefining Quality--Implications of Recent Clinical Trials*, 2537-2539, *supra* at note 20.

because of the length of trial required to attain morbidity and mortality data.⁴⁷⁵ However, there is great potential harm in failing to convert the presumed benefit of a surrogate endpoint into evidence of an actual benefit because of the potential for cardiovascular complications in the interim if patients are consuming less effective therapeutics. That is, there is an opportunity cost to taking an ineffective or under-effective therapy when proven (and perhaps less expensive) therapies exist. Also, it is unclear whether patients understand the limitations on knowledge of the long-term benefits of prescription medical products approved under a surrogate endpoint.

B. Implementation Goals - How do we get from here to there?

The broad goals of a public health information infrastructure provide policymakers with a desired endpoint. However, there are a lot of interim steps to ensure that investments in public health information infrastructure are well-spent. The implementation goals for a future infrastructure are outlined herein.

1. Legal and Regulatory Implementation Goals

Congress has appropriated monies and mandates to invest in a new public health information infrastructure, one that can be used to generate accurate postmarket information on the safety and effectiveness of prescription medical products. It has given marching orders without a map, instructing the public health agencies to take advantage of data generated in the postmarket to resolve the safety and clinical comparative effectiveness knowledge gaps that exist there. Although the FDAAA defines an adverse drug experience, a serious adverse drug experience, a serious risk, and signal of a serious risk, it fails to adequately address what the American public wants, needs, and expects in prescription medical product performance. That is, what risks are acceptable, what benefits are required, how much will it cost, and will I be have access to it? Taking for granted that premarket trials will screen out gross toxicity issues and establish a plausible biological basis of action, it is these postmarket performance targets that have not been adequately set, or even discussed. Recall from the previous chapters that individuals fear

⁴⁷⁵ B. M. Psaty and others, "Surrogate End Points, Health Outcomes, and the Drug-Approval Process for the Treatment of Risk Factors for Cardiovascular Disease," *Journal of the American Medical Association* 282, no. 8 (Aug 25, 1999), 786-790.

being subsumed into the collective when it comes to decision-making, that their varying needs will not be considered.

The most important intermediate implementation goal in developing a future public health information infrastructure is to establish a map – new prescription medical product classification scheme(s) - that recognizes that various therapeutic classes serve various purposes for various patients. On the premarket side, Subpart E approvals were intended for "life-threatening and severely debilitating illnesses"⁴⁷⁶ and Subpart H approvals were reserved for "serious or immediately life-threatening illnesses."⁴⁷⁷ The needs of these patients were distinguished and treated differently. Just as the FDA uses "standard" and "priority" classifications to distinguish approvals for unmet therapeutic needs from other needs in the premarket⁴⁷⁸, the postmarket needs a clear, organizational structure that is shared across the public health agencies and is consistent with the desires of the American public who should participate in its establishment.

In general, the postmarket evidence needs and requirements for different types of prescription medical products will vary. Expected variation might be because of utilization patterns (i.e., chronic use and acute use), disease severity, expected breadth and depth of patient populations and their particular sensitivities (e.g., pregnant women), availability of substitute products, considerations of product novelty, issues related to designated medical events, length of time following approval, etc. It is illogical to monitor all medical products in the postmarket in the same way, and yet there has been little effort to explicitly link categories or classifications of prescription medical products to particular monitoring plans. That is, the design of data collection, of data analysis techniques and study designs, of decision criteria for benefit-risk management plans such as REMS, and of coverage decisions *cannot be treated as though they are universally the same*. The point of classification is to more finely tailor a public health information infrastructure and design it in such a way as to serve wide-ranging patient care needs.

Through a public input process, patients and providers should be able to

⁴⁷⁶ Food and Drug Administration and Department of Health and Human Services, *Investigational New Drug, Antibiotics, and Biological Drug Product Regulations; Procedures for Drugs Intended to Treat Life-Threatening and Severely Debilitating Illnesses*, 41516-41524, *supra* at note 127.

⁴⁷⁷ Food and Drug Administration and Department of Health and Human Services, *New Drug, Antibiotic, and Biological Drug Product Regulations; Accelerated Approval*, 58942-58960, *supra* at note 128.

⁴⁷⁸ Food and Drug Administration, *Review Classification Policy: Priority (P) and Standard (S)*, *supra* at note 21.

communicate their value-based judgments on what constitutes appropriate safety, appropriate comparative clinical effectiveness, and appropriate cost effectiveness for variant classes. History has already established that terminal patients will accept greater safety risks and lower effectiveness margins than non-terminal patients. Classification schemes for the postmarket should reflect this judgment and should be incorporated into all aspects of postmarket action. In Congressional testimony, an FDA pharmacoepidemiologist pointed out that typical decision criteria for postmarket action are governed by the statistical significance of formal studies:

"Under [the current] paradigm, a drug is safe until you can show that, with 95 percent or greater certainty, it is not safe. That is an incredibly high, almost insurmountable barrier to overcome. It is the equivalent of beyond a shadow of a doubt. And here is an added kicker: in order to demonstrate a safety problem with 95 percent certainty, extremely large studies would be needed. Guess what? Those studies usually are not done, or they cannot be done."⁴⁷⁹

These decisions should not be delegated to regulators. The required statistical significance for a measure of safety or clinical effectiveness or cost effectiveness should be decided through a democratic process that recognizes that patient subgroups value their health in different ways.⁴⁸⁰ While it will not be possible to accommodate every individual viewpoint, the current one-size-fits-all standard is inappropriate. To show that a drug is *unsafe* with 95% certainty is not a logical outcome when children are being care for or when multiple substitute therapies exist.⁴⁸¹ A legislative process, or an administrative process with ample public participation and room for notice and comment, should address these deficiencies at the front-end of investment in a public health information infrastructure that will primarily be used in the postmarket.

When creating classification scheme(s), a reasonable line must be drawn between over-simplification and over-complication. Further, all stakeholders should resist the temptation to treat the American citizen as though (s)he were incapable of understanding such issues as statistical significance. Patients have an explicit right to know what

⁴⁷⁹ Testimony of David Graham in U.S. Senate Committee on Finance, *FDA, Merck, and Vioxx: Putting Patient Safety First?*, 17, *supra* at note 23.

⁴⁸⁰ Ashford, *The Legacy of the Precautionary Principle in US Law: The Rise of Cost-Benefit Analysis and Risk Assessment as Undermining Factors in Health, Safety and Environmental Protection*, 352-378, *supra* at note 63... there should be "Consideration of creating a sliding scale for the burden of proof – that is, the strength of data/information needed to justify taking (or stopping) action."

⁴⁸¹ Although it is beyond the scope of this paper, a significance level of .05 for efficacy in the premarket is not logical either. Patient needs are different and they should be treated as such.

decision criteria have been used to set benefit-risk ratios. This implementation goal logically precedes technical and scientific implementation goals because the generation of prescription medical product classification schemes should guide technical and scientific data collection, data analysis, benefit-risk management plans, and coverage decisions.

New classification schemes will also be of benefit to government agencies and biopharmaceutical companies because they will reduce uncertainties that affect investment decisions. There is both regulatory uncertainty and reimbursement uncertainty regarding how different therapeutics will be treated in the postmarket and how these decisions will be made. For example, recent trends in industry research and development demonstrate an exit from cardiovascular care and diabetes care markets because of uncertain postmarket monitoring requirements.⁴⁸² Testimony from FDA officials on appropriate postmarket requirements for these groups has not been reassuring:

"If you have a drug that is going to be used by large numbers of people on a chronic basis, I think you are obligated to do really large studies and follow them for a reasonably long period of time. What that 'reasonably' is, I do not know. I can tell you, it is not a month, it is not 2 months, it is not 6 months. A year might not be enough."⁴⁸³

Coverage with Evidence Development (CED) plans have also created uncertainties that could be alleviated with useful classification schemes. In terms of coverage and formulary policy, the CMS created six "protected" drug classes for Medicare Part D coverage: antidepressants; antipsychotics; anticonvulsants; immunosuppressants; HIV medications; and anticancer agents not covered under Medicare Part B. These classes are privileged because:

"restricted access to drugs in the category or class would have major or life threatening clinical consequences for individuals who have a disease or disorder treated by the drugs in such category or class," and "there is significant clinical need for such individuals to have access to multiple drugs within a category or class due to unique chemical actions and pharmacological effects of the drugs within the category or class."⁴⁸⁴

In other words, patients in these classes are more sensitive to changes in their therapeutic regimes and the drugs are not easily interchangeable. Thus, Medicare Part D

⁴⁸² Hughes, *News Feature: 2008 in Reflection*, 6, *supra* at note 399.

⁴⁸³ Testimony of David Graham in U.S. Senate Committee on Finance, *FDA, Merck, and Vioxx: Putting Patient Safety First?*, 40, *supra* at note 23.

⁴⁸⁴ Sec. 176. Formulary Requirements with respect to certain categories or classes of drugs in *Medicare Improvements for Patients and Providers Act of 2008*, Public Law 110-275, *Statutes at Large* 122 (July 15, 2008), 2494-2597, codified at 42 U.S.C. § 1395w-104(b)(3)(G).

programs are not permitted to initiate step therapy changes (i.e., start on drug X rather than drug Y for a given condition), quantity limitations, or prior authorization policies if and when these patients change coverage among competing payors. The CMS is required to revisit this "protected" class list prior to 2010 and the tiered review procedures that it established for this purpose – data analysis, expert panels, and public notice and comment – are a good starting point for a logical re-examination of future classification schemes to be adopted more broadly.⁴⁸⁵ The CMS and other agencies should strive for consistency in the way they privilege certain classes of products.

An additional, related legislative implementation goal is to remove the restrictions on government health agencies that prevent them from acting on evidence obtained through comparative effectiveness studies. Part of the push to sever coverage implications from comparative effectiveness studies was the fear of arbitrary treatment for patients that would remove therapies from coverage. These objections can be assuaged through a democratic process that establishes metrics for safety, clinical-, and cost-effectiveness on a sliding scale of burden of proof depending on the type of product being considered. For example, if terminal cancer clinical effectiveness milestones (informed by providers and patients) are set at the X statistical significance level, then postmarket data collection and analysis should be designed around achieving that level with a pre-specified statistical power. Prior to either achievement or non-achievement, decision criteria should be set that will determine issues of coverage, non-coverage, or partial coverage (i.e., preferred or non-preferred status on formularies). It is unethical to force the American public to pay for treatments that reach below the effectiveness threshold that they have contributed to creating, but this threshold does not have to be locked-in to a p value (or measure of statistical significance) that has persisted because of historical convention.⁴⁸⁶ It is not necessary to settle for binary choices that fail to recognize the diversity in treatments and the diversity in patients.

⁴⁸⁵ Centers for Medicare and Medicaid Services and Department of Health and Human Services, "Medicare Program: Medicare Advantage and Prescription Drug Programs MIPPA Drug Formulary & Protected Classes Policies," *Federal Register* 74, no. 11 (January 16, 2009, 2009), 2881-2888, <http://edocket.access.gpo.gov/2009/pdf/E9-783.pdf> (accessed May 2, 2009).

⁴⁸⁶ Ashford, *The Legacy of the Precautionary Principle in US Law: The Rise of Cost-Benefit Analysis and Risk Assessment as Undermining Factors in Health, Safety and Environmental Protection*, 372, *supra* at note 63.

2. Technology Implementation Goals

Technology implementation should logically follow-on from more complex classification schemes for prescription medical products. However, in the interim, it is not unreasonable to believe that some postmarket monitoring plans will be similar in design to the plan that Congress envisioned in the FDAAA. Technology implementation of the Congressional mandates demands significant improvements in information technology in the areas of distributed database management, networks, security, and interoperability. Specifically, the FDA must "link and analyze safety data from multiple sources with the goals of including, in aggregate...at least 100,000,000 patients by July 1, 2012."⁴⁸⁷ The million patient threshold will be met with Medicare Part D claims databases⁴⁸⁸, Department of Defense and Veterans' Health Administration databases⁴⁸⁹, and other large claims databases. Adoption of electronic health records in the U.S. is extraordinarily low⁴⁹⁰, suggesting that reliance on administrative claims data is probably most likely for the foreseeable future. All of these efforts echo the intentions of the DHHS's Nationwide Health Information Network: "to provide a secure, nationwide, interoperable health information infrastructure that will connect providers, consumers, and others involved in supporting health and healthcare."⁴⁹¹

To start to approach an engineering design, the FDA created several short-term data contracts that evaluated potential data sources and potential database models.⁴⁹² Both

⁴⁸⁷ Sec. 905: Active Postmarket Risk Identification and Analysis in *Food and Drug Administration Amendments Act of 2007, Public Law 110-85*, codified at 21 U.S.C. § 355(k)(3).

⁴⁸⁸ Centers for Medicare and Medicaid Services and Department of Health and Human Services, "Medicare Program; Medicare Part D Claims Data; Final Rule," *Federal Register* 73, no. 103 (May 28, 2008), 30671-30672, <http://edocket.access.gpo.gov/2008/pdf/08-1298.pdf> (accessed April 15, 2009). "[CMS] proposed to allow broad access for other Federal government executive branch agencies to our Part D claims data, linked to other claims data files...[CMS] will make Part D claims data available under a process that builds upon the practice that is currently in place today with respect to the release of Medicare Parts A and B data."

⁴⁸⁹ U.S. Department of Health and Human Services, Food and Drug Administration, *The Sentinel Initiative: A National Strategy for Monitoring Medical Product Safety*, 18, *supra* at note 26.

⁴⁹⁰ Jha and others, *Use of Electronic Health Records in U.S. Hospitals*, 1634, *supra* at note 383...

"Information systems in more than 90% of U.S. hospitals do not even meet the requirement for a basic electronic-records system."

⁴⁹¹ Department of Health and Human Services, "Nationwide Health Information Network (NHIN): Background," HHS, <http://www.hhs.gov/healthit/healthnetwork/background/> (accessed August 22, 2008).

⁴⁹² Contract results are being made available to the public via a docket number published in the Federal Register. See Food and Drug Administration and Department of Health and Human Services, "Availability of Information Related to the Sentinel Initiative," *Federal Register* 74, no. 87 (May 7, 2009), 21371-21372, <http://www.fda.gov/OHRMS/DOCKETS/98fr/E9-10555.htm>.

the NIH⁴⁹³ and the AHRQ⁴⁹⁴ are studying various infrastructure models that leverage existing data sets for research purposes. The NIH's most recent request for proposal related to postmarket evidence utilization was notable for its emphasis on information technology linkage and interoperability between multiple databases.⁴⁹⁵ Finally, private non-profit organizations are supporting development of common information infrastructures to monitor patient safety and quality initiatives.⁴⁹⁶

The intention of combining such large databases, either in a decentralized network or a number of central data warehouses, is twofold. First, detecting therapeutic differences between various subgroups requires a sufficient statistical power that may be impossible without a large pool of potential patient data files, especially for pharmacogenomic treatments. Second, longitudinal health data are needed to monitor the

⁴⁹³ U.S. Department of Health and Human Services and Office of Extramural Research at National Institutes of Health, *NIH Challenge Grants in Health and Science Research (RC1)*, *supra* at note 47. See particularly, 05-AG-101 - Data Infrastructure for Post-Marketing Comparative Effectiveness Studies, "The challenge is to create the data infrastructure that will enable comparisons of particular therapies, prescribing patterns, and benefit designs on health outcomes," and 10-LM-101 - Informatics for post-marketing surveillance.

⁴⁹⁴ For example, see Agency for Healthcare Research and Quality, "Developing a Distributed Research Network to Conduct Population-Based Studies and Safety," AHRQ, <http://www.effectivehealthcare.ahrq.gov/healthInfo.cfm?infotype=nr&ProcessID=54> (accessed August 15, 2008)... "To support AHRQ's Effective Health Care program, the DEcIDE centers... will develop specifications for a scalable distributed research network to support a wide array of purposes related to therapeutics, including comparative effectiveness, safety, and utilization, as well as quality of care research." Also see, Agency for Healthcare Research and Quality, "Distributed Network for Ambulatory Research in Therapeutics," AHRQ, <http://www.effectivehealthcare.ahrq.gov/healthInfo.cfm?infotype=nr&ProcessID=53> (accessed April 15, 2009), describing research that will "Demonstrate the ability to collect specific data from clinicians, staff or patients on a clinically defined set of individuals to enrich the EHR data set and answer effectiveness and safety questions concerning medical therapeutics." These two programs are also described in U.S. Department of Health and Human Services, Food and Drug Administration, *The Sentinel Initiative: A National Strategy for Monitoring Medical Product Safety*, 24, *supra* at note 26.

⁴⁹⁵ U.S. Department of Health and Human Services and Office of Extramural Research at National Institutes of Health, *NIH Challenge Grants in Health and Science Research (RC1)*, *supra* at note 47. Suggested projects include: "(1) data linkages to allow studies of diffusion of therapies and comparisons of their effects on outcomes, health care utilization and expenditures across hospital referral regions, hospitals, and physician practices; (2) Linkage of Medicaid administrative data and Medicare Part D claims data for comparative research on prescribing patterns and patient outcomes in the nursing-home population; (3) Linkage of prescription drug data to data banks such as those maintained by the Alzheimer's Disease Neuroimaging Initiative to allow comparative research on outcomes in defined patient populations;...(6) Data linking features of health and prescription drug insurance (public or private) to utilization of health services and health outcomes." (emphasis added)

⁴⁹⁶ Robert Wood Johnson Foundation, "National Effort to Measure and Report on Quality and Cost-Effectiveness of Health Care Unveiled," RWJF, <http://www.rwjf.org/pr/product.jsp?id=22371&typid=160> (accessed August 15, 2008)... "The Robert Wood Johnson Foundation will provide nearly \$16 million in grants to develop and test a single national approach to bring consistency to efforts to measure and report information on the quality and cost of care that patients receive."

responses of patients to various therapies over time (particularly, products that must be taken throughout a lifetime), and that data may be housed among several healthcare providers or claims agencies. In other words, patients are known to change providers and health plans, and it will be necessary to develop mechanisms to track patients as they move. It is notable that all of the current potential infrastructure models under consideration *rely on data that is already being collected* through insurance claims, electronic health records, registries, pharmaceutical purchases, and clinical trials.⁴⁹⁷

Two aspects of this future design are worth examining for their technical and legal implications: 1) these data are privately-owned in numerous electronic formats that exist under disparate security, privacy, proprietary, and quality assurance protocols, and 2) these data are collected for a primary purpose that is typically exclusive of research or surveillance efforts, with the obvious exception of registries and/or clinical trials. As such, much of these data must be re-purposed and "cleaned" for research and postmarket surveillance efforts. Integration of disparate databases is non-trivial. A requirement to *convert* non-standard databases to a common form is likely infeasible because of the imposition on private data owners. As a National Research Council study explains, "To exploit such data effectively, users need to be able to ask queries that span multiple data sources without requiring the data to be standardized or requiring the user to query each single database in isolation."⁴⁹⁸

In order for heterogeneous data to be integrated, these data must be mapped to each other using a consensus ontology (or data dictionary or controlled vocabulary). An ontology is a standard such that all users agree on a common understanding of concept X and annotate the components of their variant databases to reflect that agreement. For example, privately held databases are likely to record/encode the same health concept in different ways (i.e., blood pressure may be simultaneously BP). Thus, interoperability standards are needed in this infrastructure just as they have been needed in railroads,

⁴⁹⁷ See U.S. Department of Health and Human Services, Food and Drug Administration, *The Sentinel Initiative: A National Strategy for Monitoring Medical Product Safety*, 13, *supra* at note 26, "The Sentinel System... will ultimately enable us to access the capabilities of multiple, existing data systems (e.g., electronic health record systems, medical claims databases) ... [it] will build on existing systems and data, to the extent practicable, rather than create a new system."

⁴⁹⁸ National Research Council, *Computational Technology for Effective Health Care: Immediate Steps and Strategic Directions*, eds. William Stead and Herbert S. Lin (Washington, DC: National Academies Press, 2009), 10, http://books.nap.edu/catalog.php?record_id=12572.

highways, and electricity. In-depth descriptions of the specific technological challenges involved in database integration is beyond the scope of this paper; it is sufficient to say that significant effort (both time and resources) is required, but that these technical challenges are not insurmountable or without precedent.⁴⁹⁹

Presuming a consensus ontology or standard is established, additional concerns with data integration include the amount of time and effort spent "cleaning" or performing quality assurance checks when such data are used for healthcare decision-making. Quality assurance normally can be done in parallel using automated algorithms to the maximum extent permissible. The extent to which providers and other medical professionals will need to perform medical chart reviews is an open question for study. Finally, an important technological challenge is to develop automated methods such that computer algorithms will be able to identify the same patient's records if multiple records exist in various privately owned data locations.

However, emphasizing the secondary use of data begs the question: what data are *routinely needed beyond what is routinely collected* in order to develop postmarket evidence on safety and clinical effectiveness? In other words, what important data are not normally captured in claims data or in electronic health records that may be required to assess the performance of these products? How will that data be collected (i.e., can existing electronic data collection mechanisms be modified or is a new type of data collection required)? As noted earlier, the answers to these questions will differ based on whether the therapeutic to be monitored is a first-in-class type of new molecular entity or device, whether the therapeutic is administered in a clinical environment (e.g., chemotherapy) or on an outpatient basis, whether it treats a chronic or acute condition, and whether it is administered to patients who are likely to be highly sensitive as a result of previous medical history, genetics, or polypharmacy. If subgroup analyses are to be performed, it will be necessary to capture the characteristics that define the subgroup.

⁴⁹⁹ Database integration has been necessary among private corporations as the result of mergers and acquisitions since information technology systems first became widespread. For examples in public health, see the work on the Cancer Biomedical Informatics Grid (caBIG), S. Langella and others, "Sharing Data and Analytical Resources Securely in a Biomedical Research Grid Environment," *Journal of the American Medical Informatics Association* 15, no. 3 (May-Jun, 2008), 363-373; J. Saltz and others, "CaGrid: Design and Implementation of the Core Architecture of the Cancer Biomedical Informatics Grid," *Bioinformatics* 22, no. 15 (Aug 1, 2006), 1910-1916; M. C. Hornbrook and others, "Building a Virtual Cancer Research Organization," *Journal of the National Cancer Institute: Monographs* (35), no. 35 (2005), 12-25.

Gathering additional data is costly. Not only are there direct costs associated with the actual gathering, there are indirect privacy costs to the patient, and the security costs associated with safeguarding health data. Additionally, if effective postmarket evidence development requires collection of new types of data, who will own it and take responsibility for its upkeep? It is necessary for stakeholders to design a system that is both parsimonious and effective in its treatment of data. Value of information analysis in combination with decision analysis is common in the economics literature and is designed to elicit whether collection of particular data results in changed outcomes.⁵⁰⁰ Such techniques should be used for parsing out the data requirements of a future public health information infrastructure.

The technology implementation goals are largely practical. First, when secondary uses of routinely collected data are re-purposed in postmarket evidence utilization, these databases need to be able to securely and accurately "talk" to each other. These issues have been confronted in other areas such as air transportation and finance. However, the designs of technology solutions do not exist in isolation. These designs will have implications for the statistical and scientific methods utilized to analyze data, for the scalability issues when incorporating other types of databases and data types, for the governance issues surrounding control and access to the data, and for the financial issues with respect to initial investment and ultimate sustainability of the infrastructure. Second, since the data required for randomized controlled trials is so difficult and onerous to collect, many stakeholders have agreed (some reluctantly) that building technology to repurpose primary clinical data is a logical alternative. However, stakeholders need to thoroughly ask whether these two extreme options are the only available or desirable ones? Neither of these options considers a patient's ability or interest in uploading data that they collect themselves.

Biosensing wireless technologies for the elderly and other similarly homebound people are a rapidly growing area of innovation and investment. They include fall monitoring, cardiovascular monitoring, glucose monitoring, and other emergency

⁵⁰⁰ For examples in healthcare decision-making, see K. Claxton, J. T. Cohen and P. J. Neumann, "When is Evidence Sufficient?" *Health Affairs* 24, no. 1 (Jan-Feb, 2005), 95-99.

response monitoring.⁵⁰¹ These data collection devices are designed for real-time monitoring and share many of the common goals of an active surveillance system. Yet, little attention has been paid to how these devices might provide another postmarket data collection technique. Similarly, the 7000+ member community of the PatientsLikeMe.com website have been performing personal active surveillance by volunteering their private data and gaining access to the data of others in similar conditions.⁵⁰² Consequently, there are technologies available and in development that can be leveraged to make patients more active participants in assessing the safety and effectiveness of the prescription medical products they choose to utilize. Additionally, self-reported patient information could be used to understand some of the other issues patients face related to prescription medical products such as their out-of-pocket costs, their perception of the utility of the product, their likelihood to adhere to the schedule, etc. The launch of personal health records such as Google Health™ and Microsoft HealthVault™ underscore the value that patients derive from tracking their health progress.

New electronic prescription medical product tracking systems (designed to combat counterfeit or impure pharmaceuticals) are being implemented to trace a product from the point of manufacture to the point of sale.⁵⁰³ It is not hard to envision these same systems being extended to allow randomly selected patients to report on a variety of metrics regarding their use of a prescription medical product. It is perhaps as simple as attaching a website and access credentials to a product along with a request from a pharmacist to login and report performance. In general, technology implementation goals

⁵⁰¹ For example, see descriptions in J. S. Beaudin, S. S. Intille and M. E. Morris, "To Track Or Not to Track: User Reactions to Concepts in Longitudinal Health Monitoring," *Journal of Medical Internet Research* 8, no. 4 (2006), e29... "Sensors embedded in the home (and on mobile devices) are proposed to collect longitudinal and contextually sensitive data that can then be processed to automatically detect important changes in behavior patterns caused by the onset of illness."

⁵⁰² See PatientsLikeMe, "PatientsLikeMe: About Us," PatientsLikeMe, <http://www.patientslikeme.com/> (accessed April 14, 2009)... "Our goal is to enable people to share information that can improve the lives of patients diagnosed with life-changing diseases. To make this happen, we've created a platform for collecting and sharing real world, outcome-based patient data." For a narrative on a patient's experience with examining the data available in order to inform medication choices, see commentary in Thomas Goetz, "Practicing Patients," *The New York Times Magazine*, March 23, 2008.

⁵⁰³ Food and Drug Administration and Department of Health and Human Services, "Prescription Drug Marketing Act Pedigree Requirements Under 21 CFR Part 203 Compliance Policy Guide and Guidance for Industry: Prescription Drug Marketing Act Pedigree Requirements Questions and Answers; Notice of Availability," *Federal Register* 71, no. 220 (November 15, 2006), 66448-66450, <http://www.fda.gov/OHRMS/DOCKETS/98fr/06-92111.htm>.

for a future public health information infrastructure must consider, study, and pilot a wide variety of data collection options.

On a systems level, technology platforms and improved research methodologies *must be co-developed* in order for new public health information infrastructure to be successful. Public agencies, pharmacoepidemiologists, providers, pharmacists, patients, and the health information technology community must work together to develop postmarket evidence technical standards in order to rely on the ability to collect the desired information electronically. Data collection must also be seamlessly incorporated into analytic platforms to allow for the conversion of postmarket data into usable knowledge by decision-makers.

3. Scientific Implementation Goals

The goals in scientific implementation are closely tied to those in technical implementation and center around one idea: what kind of data analyses based on what kind of data are needed for what type of drug in the postmarket? Since the formal introduction of the concept of evidence-based medicine in the 1990s, there has been considerable debate about what types of studies constitute high-quality evidence.⁵⁰⁴ In 2004, David Graham, a pharmacoepidemiologist at FDA bemoaned a "culture [that] is dominated by a world view that believes only randomized clinical trials provide useful and actionable information."⁵⁰⁵ Particularly, there has been debate over the degree to which study designs that rely on observational data can be substituted for randomized clinical trials (RCTs), considering by many to be the gold standard of evidence.⁵⁰⁶ RCTs are typically the apex of evidence hierarchies because of their ability to prove causality

⁵⁰⁴ See discussion in U.S. Office of Technology Assessment, *Identifying Health Technologies that Work: Searching for Evidence*, *supra* at note 30; Anderson, *Measuring what Works in Health Care*, 1080-1082, *supra* at note 32.

⁵⁰⁵ Testimony of David Graham in U.S. Senate Committee on Finance, *FDA, Merck, and Vioxx: Putting Patient Safety First?*, 16, *supra* at note 23.

⁵⁰⁶ In 2000, the debate was re-ignited by two papers that found no difference in estimates of treatment effects between the two types of studies. For more, see J. Concato, N. Shah and R. I. Horwitz, "Randomized, Controlled Trials, Observational Studies, and the Hierarchy of Research Designs," *The New England Journal of Medicine* 342, no. 25 (Jun 22, 2000), 1887-1892; K. Benson and A. J. Hartz, "A Comparison of Observational Studies and Randomized, Controlled Trials," *The New England Journal of Medicine* 342, no. 25 (Jun 22, 2000), 1878-1886.

(as opposed to correlation or association).⁵⁰⁷ Recall from chapter one that RCTs in the postmarket are described as pragmatic or practical clinical trials (PCTs). PCTs avoid many of the criticisms that premarket clinical trials face because they 1) seek to answer questions of clinical relevance about the risks, benefits, and costs of various interventions relative to substitutes; 2) they enroll diverse study populations; 3) they recruit patients from a variety of practice settings (i.e., beyond academic medical centers); and 4) they measure a broad range of relevant health outcomes including quality of life, patient satisfaction with treatment, morbidity and mortality, etc.⁵⁰⁸ PCTs are similar to their premarket counterparts in that they are expensive to conduct and they are well-accepted to be methodologically robust.

Observational data, on the other hand, are derived from administrative claims data, registries, and electronic health records. In the current environment, as indicated in the preceding section, Congress, academics, public agencies and other stakeholders have indicated that observational data will be the new engine of clinical research. Data are typically more abundant and inexpensive, but analyses are less robust, less precise and prone to confounding and selection bias errors.⁵⁰⁹ With observational data or a non-randomized design, it is difficult to determine whether outcomes should be attributed to inherent differences in patients or differences in treatment, especially when patients may be steered toward a particular treatment *precisely because* a provider has reason to believe it will be more effective. Worse, observational data and randomized studies do not always provide the same results. Most famously, the results of the Women's Health Initiative trial – a PCT - overturned the results and recommendation of numerous previous observational studies, but at a taxpayer cost of \$725M.⁵¹⁰

Compare that amount with the \$1.1B new monies allotted for comparative research

⁵⁰⁷ See, for example, Agency for Healthcare Research and Quality, *U.S. Preventive Services Task Force Grade Definitions*; Guyatt and others, *GRADE: An Emerging Consensus on Rating Quality of Evidence and Strength of Recommendations*, 924-926, both *supra* at note 377.

⁵⁰⁸ Tunis, Stryer and Clancy, *Practical Clinical Trials: Increasing the Value of Clinical Research for Decision Making in Clinical and Health Policy*, 1624-1632, *supra* at note 13.

⁵⁰⁹ See Schneeweiss, *Developments in Post-Marketing Comparative Effectiveness Research*, 143-156, *supra* at note 427; and Testimony of David Graham in U.S. Senate Committee on Finance, *FDA, Merck, and Vioxx: Putting Patient Safety First?*, 33, *supra* at note 23.

⁵¹⁰ Rossouw and others, *Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women: Principal Results from the Women's Health Initiative Randomized Controlled Trial*, 321-333, *supra* at note 188. For price information, see Institute of Medicine (IOM), *The Future of Drug Safety: Promoting and Protecting the Health of the Public*, 115, *supra* at note 15.

and it is not hard to understand why some have deemed the dependence on randomized trials in the current clinical research enterprise to be a failure of the system.⁵¹¹ They believe that getting more frequent but lower quality information more than makes up for the long waiting times required for the highest quality information. The IOM's major criticism of randomized controlled trials is the capacity constraint on supply because of the expense involved.⁵¹² It is simply infeasible to perform enough RCTs quickly enough to make a dent in resolving the incomplete information on the safety and clinical effectiveness of prescription medical products. Congress also acknowledged this reality by ordering the FDA to answer questions on postmarket safety proceeding from the least resource-intensive solutions to the most-resource intensive. Specifically, outstanding questions of postmarket safety must be answered first using the spontaneous reporting system and active postmarket risk identification and analysis system if possible, followed then by "postapproval studies," and finally, by postapproval clinical trials.⁵¹³

However, as was true with the technology implementation goals, it is important to not focus narrowly on these two methodologies as the *only* available choices just because they are the most familiar. For example, environmental epidemiologic surveys are driven by systematic sampling methods, which randomize the population to be studied but not necessarily the exposure. Economists use proxy variables or instrumental variables to overcome confounding errors. There are likely many potential investigational designs, possibly from other fields, that could represent useful solutions. Postmarket methods, analysis algorithms, sampling techniques, and study designs are immature.⁵¹⁴ It is an area of study that has not received as much attention as it deserves. Recognizing the imbalance, Congress directed the newly created Chief Scientist at the FDA to “develop postmarket safety performance measures that are as measurable and rigorous as the ones already developed for premarket review.”⁵¹⁵ All issues considered, the IOM's comments

⁵¹¹ Tunis, Stryer and Clancy, *Practical Clinical Trials: Increasing the Value of Clinical Research for Decision Making in Clinical and Health Policy*, 1624-1632, *supra* at note 13.

⁵¹² Institute of Medicine (IOM), *Learning Healthcare System Concepts v2008: Annual Report*, iv, *supra* at note 57.

⁵¹³ Sec. 905: Active Postmarket Risk Identification and Analysis in *Food and Drug Administration Amendments Act of 2007*, Public Law 110-85, codified at 21 U.S.C. § 355(o)(3)(D).

⁵¹⁴ Avorn, *In Defense of Pharmacoepidemiology--Embracing the Yin and Yang of Drug Research*, 2221, *supra* at note 107.

⁵¹⁵ Sec. 910: Office of the Chief Scientist in *Food and Drug Administration Amendments Act of 2007*, Public Law 110-85, codified at 21 U.S.C. § 399a(b)6.

on the matter summarize the major scientific implementation goal of a future public health information infrastructure:

"For the future of clinical effectiveness research, the important issues relate not to whether randomized experimental studies are better than observational studies, or vice versa, but to what's right for the circumstances, and how the capacity can be systematically improved."⁵¹⁶

In other words, research into new methodologies should address boundary conditions and decision points: when and how safety and effectiveness questions can be adequately addressed. *These answers will differ depending on the type of therapeutic in question.* It is here that more logical classification schemes of prescription medical products enable postmarket data collection and data analysis plans. Both establishing classification schemes and then linking certain forms of data collection, data analysis, and benefit-risk management plans to them requires value judgments related to expectations of the benefit and risk of these prescription medical products. Only when these guideposts are clearly laid out can scientists and engineers begin working together to devise technical and scientific solutions.

4. Organizational/Institutional Implementation Goals

A public health information infrastructure populated by patient data is a public good, one in which the benefits and costs are shared by all participants. Such a precious resource requires the thoughtful design of an organizational structure with the capacity, the independence, and the will to operate it on behalf of the people. As discussed in the previous chapter, the lack of insularity from political and industry pressures among the currently constituted public health agencies means that none are suited to this task. The institutional implementation goal is to build a commission-like organizational structure with similar standing to the Federal Reserve Board.⁵¹⁷

A singular public authority is best equipped to navigate the transaction costs associated with the security, legal, proprietary, and privacy barriers that accompany

⁵¹⁶ Institute of Medicine (IOM), *Learning Healthcare System Concepts v2008: Annual Report*, 31, *supra* at note 57.

⁵¹⁷ Most recently, former Senator Thomas Daschle has espoused this notion. He proposes creating a Federal Health Board, similar to the Federal Reserve System, whose structure, functions and enforcement capability would be largely insulated from the politics. See Thomas Daschle, Scott S. Greenberger and Jeanne M. Lambrew, *Critical: What we can do about the Health-Care Crisis* (New York: Thomas Dunne Books, 2008).

requests to access large amounts of patient data from a multitude of private data owners.⁵¹⁸ Barbara Evans has noted that Congress, in calling for an active postmarket risk identification and analysis system with data from one hundred million patients, has created a classical infrastructure regulator:

one that "allows private ownership of infrastructure but grants the regulator the legal authority: (1) to control market entry and exit by entities that will operate and/or use the infrastructure, and (2) to set terms governing how the approved entrants will do business, so as to serve a general public interest and/or to protect a specific vulnerable class."⁵¹⁹

If agencies outside of the FDA will need and use similar data, it is clearly inefficient for each of them to pursue data networks individually. Data owners - especially large claims owners, pharmacy benefit managers, hospital organizations - might find it infeasible or undesirable to participate in multiple networks because of the overhead load in technical and legal requirements. An advantage of a singular infrastructure is that it reduces demands on original data owners. A single resource also avoids developing redundant data models, ontologies or controlled vocabularies. It standardizes data quality checking and validation and enables development of reusable libraries of analytic programs. Such a common infrastructure has the potential to save time, effort, and cost by avoiding duplicative or redundant efforts. Accessing these data to generate collective knowledge on the safe and effective real-world use of prescription medical products requires a paradigm change: one that privileges a unified and cohesive systems-level approach above the fragmented efforts of numerous public and private stakeholders. This cohesive approach extends to utilizing a singular drug classification scheme across the agencies to influence decision-making and to drive technical and scientific direction.

Logically, the similarities in the required data favor a single, multi-purpose effort that is shared across the agencies. This infrastructure should support the FDA's active surveillance system, the CMS's patient registries to support their Coverage with Evidence Development programs, vaccine surveillance conducted by the Centers for Disease Control and Prevention, or postmarket randomized controlled trials conducted under the

⁵¹⁸ Evans, *Congress' New Infrastructural Model of Medical Privacy*, 595-596, *supra* at note 55... "It is infeasible for a private, commercial database operator to obtain all the individual authorizations (or waiver of authorizations) that would be needed to obtain identifiable information for 25 to 100 million people. Moreover, even if private entities could assemble such a database, it would need ongoing regulation to protect the privacy of persons whose data are included."

⁵¹⁹ *ibid.*, 600.

auspices of the AHRQ, the Veterans Health Administration, or the NIH. Shared knowledge is a key organizational advantage among public agencies with common goals. To draw a dramatic parallel, lack of intelligence sharing among the fifteen intelligence agencies is attributed as partial cause of the 9/11 disaster. Public health goals should not face the same sort of fragmentation.

A legislative initiative to shape the organizational structure appropriate to manage this public health information infrastructure is needed. The debate should not only focus on questions of governance, but also questions of finance. In order for the infrastructure to be sustainable, a permanent source of government appropriations paid out of the general budget or specific taxes (i.e., fee per prescription shared by public and companies) is required. Much of this funding will need to be reallocated to the original data owners for maintenance, security, and oversight through contracts. Special consideration needs to be paid to the fact that many of these data owners will be private parties that may perceive significant security and confidentiality risks in participating.⁵²⁰ For example, if a data breach occurs while a public health agency is leveraging the infrastructure for public health surveillance, who is legally liable? When can a private contractor terminate their participation in the program? Contracting vehicles will need to carefully negotiate the rights and responsibilities of all parties with respect to entry and exit; without these considerations, maintaining such an infrastructure is unsustainable. Careful incentive structures should be built to encourage continued, long-term participation without creating a monopoly structure such that one participant's withdrawal of data from the system could be catastrophic for its continued operations. Experience operating the Vaccine Safety Data Link (VSDL)⁵²¹ – a similar public health information infrastructure supported through public funds but maintained by private health care plans - should be leveraged for the design of governance and funding issues.⁵²²

⁵²⁰ Sec. 905: Active Postmarket Risk Identification and Analysis in *Food and Drug Administration Amendments Act of 2007, Public Law 110-85*, codified at 21 U.S.C. § 355(k)(3)(C)(i)(III)... "to provide for active adverse event surveillance using the following data sources, as available: (aa) Federal health-related electronic data (such as data from the Medicare program and the health systems of the Department of Veterans Affairs); (bb) private sector health-related electronic data (such as pharmaceutical purchase data and health insurance claims data); "

⁵²¹ See Centers for Disease Control and Prevention, "Vaccine Safety," CDC, <http://www.cdc.gov/vaccinesafety> (accessed August 15, 2008).

⁵²² See Institute of Medicine (IOM), *Vaccine Safety Research, Data Access, and Public Trust* (Washington, DC: National Academies Press, 2005), <http://www.nap.edu/catalog/11234.html>.

Finally, an organizational goal must be to immediately begin working toward an oversight structure for such a system. Patient data are a public good and national resource, a situation that favors creating an external oversight body separate from the agency tasked with the day-to-day operations of the system. That is, if the system is run by the Department of Health and Human Services, then another agency – perhaps the Institute of Medicine – should be funded for a permanent oversight function. This type of structure enhances the credibility of the organization charged with operating it. The oversight organization would be charged with routing auditing of security, data access, and privacy issues. It could also add leadership on creating conflict-of-interest policies, privacy and human subjects protection policies, and other requirements.

5. Social Implementation Goals

The foremost social implementation goal for development of a future health information infrastructure is to begin a dialogue with the American public about the benefits and risks of their participation in such a system. The full extent of patient privacy and security concerns is yet unknown because the system is not tangible enough to patients to envision the specific uses of it. Patients need to understand: how will their records (administrative or clinical or self-reported) be used in such an infrastructure? Will they be consented for these uses or will they fall under the public health surveillance exceptions of the Health Insurance Portability and Accountability Act (HIPAA)? Would patients be willing to allow their longitudinal health data to be connected across disparate data owners? Another goal is to establish institutional incentives to garner the participation of providers (including nurses, pharmacists, and homecare specialists) and patients in the careful monitoring, reporting, and management of prescription medical product use. These incentives could be financially tied to reimbursement or malpractice insurance, or could be administratively tied to prior authorization or licensure. The historical failures of systems without behavioral incentives *built-in* underscores this need.

6. Private Sector Implementation Goals

Despite the excitement over the new public health information infrastructure, there is still a lot of unfinished business in the postmarket resulting from years of neglect. Most glaringly, the number of outstanding postmarket study commitments based on the

approval of surrogate endpoints needs to be promptly reviewed for new regulatory actions.⁵²³ For postmarket study commitments that were voluntarily agreed to – and are effectively unenforceable – the FDA should immediately look to Congress to expand the use of agency-administered exclusivities described in chapter three.⁵²⁴ There are large opportunity costs at stake for patients taking yet unproven therapies, and these patients make up large subpopulations since surrogate endpoints have been frequently used with blockbuster products. Additionally, the CMS should consider privileging products that have developed data on primary endpoints to hold special status on reimbursement formularies. Finally, as more prescription medical products become generic, it is possible for products *that have never shown results relevant to primary endpoints* to become postmarket "orphans." That is, the original sponsor will no longer care to produce information on these products because they will not be able to capture rewards from producing this information. Again, exclusivity policies should be implemented to capture the desired information.

Biopharmaceutical companies have responded to the perceived uncertainty in postmarket shifts in potentially harmful ways for patients. Consider this news report on Schering-Plough:

"Chief Executive Fred Hassan and his top scientists have pulled the plug on two drug-development projects -- one for obesity and the other for cholesterol -- that had the potential to produce big sellers. And they're considering scrapping a third. The reason: Mr. Hassan believes an intensifying focus on safety and a diminished tolerance for side effects at the Food and Drug Administration have dramatically lowered the odds that the drugs would make it to market -- at least not without a lot of extra time and money."⁵²⁵

Clearly, the FDA and biopharmaceutical companies are not communicating well. New changes in the postmarket environment should not mean *a priori* that prescription medical products with a high potential for safety issues should be abandoned; they have a likelihood of success *if they answer an unmet therapeutic need or provide some other comparable benefit*. The use of rigorous postmarket requirements to bring a truly innovative product to patients is as old as 1970 with the Levodopa case discussed in

⁵²³ Center for Drug Evaluation and Research, Food and Drug Administration, *Postmarketing Study Commitments*, *supra* at note 268.

⁵²⁴ See policy suggestions in Wood, *A Proposal for Radical Changes in the Drug-Approval Process*, 620-622, *supra* at note 214.

⁵²⁵ Johnson and Winslow, *Side Effect: Drug Makers Say FDA Safety Focus is Slowing New-Medicine Pipeline*, 1, *supra* at note 371.

chapter two and has been furthered through Subpart E and H approvals. In 1975, the FDA Commissioner stated:

"Since approval is our last chance, we properly now tend to want all data in hand to be absolutely certain of every detail before approving a drug...Expanded post-marketing authority might permit earlier appearance in the U.S. of many drugs, in return for a longer investigational phase control by FDA."⁵²⁶

The Levodopa model worked and should be used more broadly on the most innovative products with the potential to make a significant difference in unmet needs.

7. Summary of Implementation Goals

Overall, the interim goals for building a "greenfield" public health information infrastructure dedicated to the postmarket performance of prescription medical products are:

- Develop logical prescription medical product postmarket classification scheme(s) – ones that reduce uncertainty by creating expectations about appropriate postmarket actions to learn about a product's safety and clinical effectiveness in real-world populations.
- Explore technological and scientific solutions that follow on from these classifications. Do not limit options to the conventional reliance on randomized controlled trials or observational epidemiology. It does not have to be an either-or scenario. Do not be imprisoned by conventional notions of statistical significance. One size does not fit all.
- Create an independent, singular public health authority to manage such an infrastructure and allow it to be shared by the current public health agencies. Charter it to be politically insulated from politics and undue private influences. Create a strong oversight organization that is independent of this public health authority to enhance system-level credibility.
- Address issues of governance and funding with private data owners immediately.

⁵²⁶ U.S. Department of Health, Education, and Welfare, *Review Panel on New Drug Regulation: Final Report* (Washington, DC: DHEW, 1977), 92, quoting Alexander M. Schmidt, Commissioner of FDA, Tulane University School of Medicine, Symposium on Principles and Techniques of Human Research and Therapeutics, New Orleans, LA, Nov 5, 1975.

- Engage the public on issues concerning new classification schemes and their implications for postmarket requirements. Create incentive structures to encourage public and provider participation in future postmarket data collection.
- Take care of the unfinished business of backlogged postmarket commitments. Engage biopharmaceutical companies to develop high-risk and innovative products by using the new postmarket infrastructure as a safety net.

VI. Policy Strategies

Carrying out the broad goals outlined in the previous chapter is a significant undertaking. Stakeholder dialogue on these matters must begin immediately and institutional incentive structures must be built into the future development of a public health information infrastructure in order to achieve the desired goals.

A. *Regulatory Strategies*

Congress called on the FDA to consider the following factors when proposing a REMS strategy in the postmarket:

- (A) The estimated size of the population likely to use the drug involved.
- (B) The seriousness of the disease or condition that is to be treated with the drug.
- (C) The expected benefit of the drug with respect to such disease or condition.
- (D) The expected or actual duration of treatment with the drug.
- (E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.
- (F) Whether the drug is a new molecular entity.⁵²⁷

This is a logical starting point for serious postmarket classification scheme(s) and this sort of analysis should be applied to every class of prescription medical product. Some potential additions include consideration of any special or at-risk populations such as children, pregnant women, the elderly, immunocompromised patients, or those deemed extraordinarily sensitive (i.e., CMS's designation of "protected classes"); and consideration of available substitutes. This list of classifications may be too long or too short, but it should be vetted with stakeholders (including all the public health agencies) to determine which designations are the most overriding when considering postmarket regulatory strategies. For example, is a cancer patient primarily designated by the seriousness of their disease? It probably depends on whether it is terminal.

Once draft classification schemes are developed for vetting, patient focus groups should be conducted using appropriate social science survey methods that seek to understand the needs of these populations and their relative risk-aversion/risk-tolerance. Draft safety and comparative clinical effectiveness targets should be set on the basis of

⁵²⁷ Sec. 905: Active Postmarket Risk Identification and Analysis in *Food and Drug Administration Amendments Act of 2007, Public Law 110-85*, codified at 21 U.S.C. § 355-1(a)(1)(A).

these focus groups with the aid of providers. These targets should be unambiguous, broad, and quantifiable. Perhaps they will be "check" points – interim in nature – or ultimate goals. The bottom line is that patients need to be heard. For example, diabetics should have a voice in defining what "safe" and "effective" means for them. The classification scheme(s) and working targets should be published for notice and comment. The point of establishing scheme(s) is to link them to reasonable postmarket monitoring plans that match the needs of the patients to the tools available in the postmarket. For example, under the Subpart H regime (designated for patients with serious or immediately life-threatening illnesses), a Subpart H approval automatically invoked a formal postmarket study requirement. All prescription medical products should have a similar base or general mapping between the class of product and the postmarket plans. These classification schemes and plans must necessarily be flexible in time. It may be hard to argue in 2009 that patients with human immunodeficiency virus (HIV) are in a situation that is immediately life-threatening if they are already on a standard care regimen. It is possible that stakeholders may jointly decide that no postmarket plan is necessary for certain classifications.

Either way, such a mapping is a blueprint for engineers, statisticians, and scientists to build or utilize the planned infrastructure to collect postmarket data in a way that corresponds to the desired analytical method. This analysis should produce quantifiable safety and effectiveness outcome results that can be relayed to decision-makers. "Decision-makers" should be interpreted broadly. These results should be available to government agencies, industry, providers, and patients. The goal is to give decision-makers information *that will materially affect their choices*; otherwise, there is little gained from gathering and analyzing the information in the first place. Because the proposed process (i.e., fairly standard postmarket plans connected to categories of prescription medical products) is a dramatic departure from normal operations, several pilot programs in unique therapeutic areas are suggested so that the process can be rigorously studied. These pilots should iterate on the classification schemes and improve them as necessary through feedback and adaptation.

In order for postmarket strategies to be effective, stakeholders need a full range of available options. Earlier versions of the FDAAA included a broad moratorium on DTCA

and the ability to use a special symbol to denote drug's status.⁵²⁸ These provisions were removed from the final version of the legislation. The constitutionality of such issues as they relate to free speech is beyond the scope of this paper, although the generality of the moratorium was considering the most challenging legal issue. Nonetheless, advertising limitations – judiciously invoked – should not be prohibited. To some extent, this regulatory option is already possible if the product has a black box warning.⁵²⁹ It is not antithetical to public health goals to limit broad advertisement of prescription medical products designated as high-risk. The main point is that stakeholders should not be constrained in their thinking; in fact, they should attempt to be as catholic as possible.

B. Organizational/Institutional Strategies

In the executive branch, as currently constituted, there is only one logical place to situate a large public health information infrastructure used by multiple agencies: in the Department of Health and Human Services (DHHS). The DHHS is best equipped to balance and coordinate the needs of subordinate agencies that will use this infrastructure to carry out their postmarket responsibilities. However, this arrangement is the less desirable option. The head of the DHHS serves at the pleasure of the President and is subject to frequent political cycles and leadership changes. Although a cabinet level position merits high status, it is not adequately insulated and independent. A better option is to start afresh by chartering an entirely new infrastructure. When designed a center for comparative effectiveness only, several government officials have advocated for a new agency over placing the responsibilities in an existing one.⁵³⁰ In developing a new organization, Congress should consider the following characteristics:

- Is a "commission" structure desirable?
- Are staggered term appointments that are non-coincident with the political cycle desirable?
- Are "whistleblower protections" designed to protect dissenting scientific voices appropriate?
- Will it be possible to remove a commissioner for something other than cause?

⁵²⁸ M. Shuchman, "Drug Risks and Free Speech--can Congress Ban Consumer Drug Ads?" *The New England Journal of Medicine* 356, no. 22 (May 31, 2007), 2236-2239.

⁵²⁹ See Testimony of David Graham in U.S. Senate Committee on Finance, *FDA, Merck, and Vioxx: Putting Patient Safety First?*, 27, *supra* at note 23.

⁵³⁰ Baucus (D-MT), *Comparative Effectiveness Research Act of 2008 (S 3408)*, 7908-7966; Wilensky, *Developing a Center for Comparative Effectiveness Information*, w572-85, *supra* at note 30.

- How will the commission be held accountable? Is an external oversight structure needed?
- How will the commission liaise with the various public health agencies that would utilize the infrastructure?
- What sort of public disclosure will be required for decision-making process?

In the interim time, the Federal Coordinating Council for Comparative Effectiveness Research may be a logical body to take ownership over the development of the infrastructure until it can be turned over to its future home. This strategy would mean removing the current responsibilities from the FDA as the lead agency and reassigning them to the Federal Coordinating Council.

The operating organization, when chartered, should include the civil servants in the "science" branches of the various agencies that utilize postmarket information. That is, the Sentinel System activities currently prescribed to the FDA and the comparative effectiveness activities that are currently ongoing in the NIH, the AHRQ, and other agencies should be consolidated under this new umbrella organization. CMS and CDC employees should also transition over to this new organization if it is logical to do so. Even if a transition is not deemed necessary, there should be formal and active liaisons from the decision-making apparatus of each of the public health agencies to the institution charged with operating the infrastructure.

C. Scientific and Technical Strategies

With the current funding available for research and future funding on the horizon via foundations and other public sources, there is no reason to delay beginning a robust research program in methodologies. These programs should seek to identify alternative methodologies with an eye to matching the postmarket problem more closely to an appropriate analytical solution. Such programs should take advantage of advances in computational modeling, mobile information communication technologies, and patient-controlled records in repositories such as Google Health and Microsoft's HealthVault. Small pilot programs should be run to develop these tools and they should be compared to results obtained by more traditional approaches.

Part of this research effort should be focused on developing a training pipeline for the next generation of scientists and epidemiologists that will be capable of developing new algorithms using parsimonious data inputs to gain knowledge in the postmarket. This

strategy is envisioned primarily in the academic sector working closely with the government agencies tasked with implementing and/or using the tools that are created. Interdisciplinary programs that bring together clinical pharmacology, statistics, epidemiology, and health information technology should be supported through grants.

Currently, the Observational Medical Outcomes Partnership (OMOP) privately funds the bulk of the methodology-based research to mitigate the known errors in nonrandomized observational data. Recall that the funding of OMOP is heavily industry-based. Public monies, either distributed by the FDA or the Federal Coordinating Council, also should be funding this research. That is, the American public should not have to rely on the methodological results derived under the supervision of biopharmaceutical companies who obviously have a vested interest in how observational data will be interpreted. Further, with the FDA as a partner to the OMOP project, it should insist that any results from methodologic research are publicly available for academic and scientific peer review.

D. Public Engagement Strategies

The public needs to be treated with respect with regard to voicing their opinions on matters related to their health, specifically their demands for safety, clinical- and cost-effectiveness in the postmarket. They need to be empowered with information to be an equal decision-maker in their care. Engagement starts by taking advantage of the leaps in information and communications technology that the public routinely uses to stay connected to issues that are important to them. Further, "health" education classes in high schools should mandate curricula that promote training in health literacy with respect to reading and understanding the major sections of prescription medical product labels and/or patient package inserts. This training should include some basic discussions on the concepts of risks and benefits with respect to medications. Particularly, it should include some elementary demonstrations on what statistical significance means through the use of teaching aids, visualization, and other techniques.

E. Cleaning up the Old Legacy

All prescription medical products approved using "surrogate or proxy endpoints" for efficacy, which have active and incomplete postmarket commitments, should be immediately reviewed. Ethically, the FDA and providers should communicate with these

patients to make clear the degree of uncertainty linking the surrogate endpoints to the primary endpoint (i.e., changes in morbidity, mortality, or quality of life).

To generate research and development to fulfill unmet needs in high-risk areas, the FDA should consider granting "priority" status, agency-administered exclusivity or some other economic incentives to biopharmaceutical companies to develop high-risk products in underserved areas like neurodegenerative diseases. However, such incentives should carry with them the requirement for participation in an appropriate REMS program to ensure continual data development in the postmarket. The pediatric exclusivity provisions, mentioned in chapter 3, provide an excellent model for the tradeoff necessary between longer periods of monopoly but more extensive postmarket data monitoring requirements.

VII. Concluding Comments

Safe and effective prescription medical product performance varies with a patient's genes, condition, environment, and lifestyle. A product's true clinical value reveals itself over time and these data may change the "known" safety and effectiveness profile of the product relative to substitutes. It is the accurate *collection and conversion of these data into usable knowledge and actionable decision points* that saves social and personal costs to the healthcare system.

The development of a future public health information infrastructure is imminent. This paper suggested several important policy goals that should be part of these future plans. They include the development of improved classification scheme(s) for prescription medical products in the postmarket; the development of a new corps of engineers and scientists working on innovative methodologies to enhance data collection and analysis in the postmarket; the creation of an independent public health authority to manage the new infrastructure; the development of logical governance and financing mechanisms to operate such an infrastructure; the immediate engagement with the American people on matters related to the prescription medical products they consume; and the legislative authority to establish incentive structures for biopharmaceutical companies to develop innovative, potentially-high risk products in areas of unmet need.

The time to act is now so that the American people can trust - and better understand and value - the risks, benefits, costs, safety, and effectiveness of the prescription medical products they use relative to appropriate substitutes. A supportive infrastructure that responds to patient needs will improve their choices regarding their utilization, and thereby reduce unnecessary costs to health.

Appendix I - List of Acronyms

ADE	Adverse Drug Experience or Event
ADR	Adverse Drug Reaction
AERS	Adverse Event Reporting System
AHCPR	Agency for Healthcare Policy and Research
AHRQ	Agency for Healthcare Research and Quality
ALLHAT	Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial
AMA	American Medical Association
ARRA	American Recovery and Reinvestment Act of 2009
BLA	Biological License Application
CATIE	Clinical Antipsychotic Trials of Intervention Effectiveness
CATT	Comparison of Age-related Macular Degeneration Treatments Trial
CBO	Congressional Budget Office
CDC	Centers for Disease Control and Prevention
CDER	Center for Drug Evaluation and Research
CED	Coverage with Evidence Development
CERTs	Centers for Education and Research on Therapeutics
CMS	Centers for Medicare and Medicaid Services
DDE	Division of Drug Experience
DHHS	Department of Health and Human Services
DTCA	Direct-to-Consumer Advertising
EBM	Evidence-based Medicine
ESAs	Erythropoiesis-stimulating agents
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDCA	Federal Food Drug and Cosmetic Act
fNIH	Foundation for the NIH
GAO	General Accounting Office or Government Accountability Office
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus

ICH.....International Conference on Harmonization of Technical Requirements for
 Registration of Pharmaceuticals for Human Use
 INDInvestigational New Drug
 IOM.....Institute of Medicine
 NASNational Academy of Sciences
 NICENational Institute for Clinical Excellence
 NIHNational Institutes of Health
 NCDNational Coverage Decision
 NDANew Drug Application
 NME.....New Molecular Entity
 NRCNational Research Council
 OIGOffice of the Inspector General
 OMOPObservational Medical Outcomes Partnership
 ONDOffice of New Drugs
 OSE.....Office of Surveillance and Epidemiology
 OTAOffice of Technology Assessment
 PCTs.....Practical or Pragmatic Clinical Trials
 PDUFAPrescription Drug User Fee Act
 PLAS.....Performance-linked Access System
 R&D.....Research and Development
 RCT.....Randomized Clinical Trials
 REMS.....Risk Evaluation and Mitigation Strategy
 RiskMAPRisk Minimization Action Plan
 SCHIPState Children's Health Insurance Program
 sNDASupplemental New Drug Application
 SSRISelective Serotonin Reuptake Inhibitors
 VA.....Veterans Administration
 VHA.....Veterans Health Administration
 VSDLVaccine Safety Data Link
 WHI.....Women's Health Initiative

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