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# All that is Gold Does Not Glitter in Human Clinical Research: A Law– Policy Proposal to Brighten the Global “Gold Standard” for Drug Research and Development

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# All that is Gold Does Not Glitter in Human Clinical Research: A Law-Policy Proposal to Brighten the Global “Gold Standard” for Drug Research and Development

Michael J. Malinowski & Grant G. Gautreaux<sup>†</sup>

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## Abstract

This Article challenges the global science standard for putting new drugs on pharmacy shelves. The primary premise is that the “gold standard” of group experimental design is an antiquated extension of drug development’s crude-science past, and is inconsistent with the precision of contemporary genetics—the science that increasingly dominates the drug development pipeline. The Article identifies law-policy options that would raise the standard for human clinical research under the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.

## Introduction

The endeavor of biopharmaceutical research and development (R&D) never has been so global—a trend complemented by collaborations that cross borders and the realization of ever-increasing international harmonization of human clinical trial research norms. Through the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), government and industry representatives have established shared standards for human clinical research<sup>1</sup> to access the three largest pharmaceutical markets: the United States, Europe, and Japan.<sup>2</sup> The primary goals of these standards are the reduction of duplication and waste in clinical research, the research needs of innovative drug developers, and the drug developers’ demand for human clinical trial data.<sup>3</sup>

The United States-based drug development industries are now outsourcing most of their clinical research to contract research organizations (CROs)—companies in the business of providing clinical research services that access health care networks outside of the United States.<sup>4</sup> Conse-

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1. See generally E9 Guidance on Statistical Principles for Clinical Trials, 63 Fed. Reg. 49,583 (Sept. 16, 1998) [hereinafter E9 Guidance]; INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE, ICH HARMONISED TRIPARTITE GUIDELINE: GUIDELINE FOR GOOD CLINICAL PRACTICE E6(R1) (1996), available at [http://www.ich.org/fileadmin/Public\\_Web\\_Site/ICH\\_Products/Guidelines/Efficacy/E6\\_R1/Step4/E6\\_R1\\_Guideline.pdf](http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step4/E6_R1_Guideline.pdf) [hereinafter ICH GUIDELINES]. For more information about the ICH, visit the official Internet site ICH, <http://www.ich.org> (last visited Oct. 3, 2011) [hereinafter ICH WEBSITE].

2. The United States is the largest pharmaceutical market, followed by Europe. See W. John Thomas, *The Vioxx Story: Would it Have Ended Differently in the European Union?*, 32 AM. J.L. & MED. 365, 375 (2006).

3. See E9 Guidance, *supra* note 1, at 49,583.

4. See Robert M. Califf, *Clinical Trials Bureaucracy: Unintended Consequences of Well-Intentioned Policy*, 3 CLINICAL TRIALS 496, 497 (2006); Miho Nagano, *Big Pharma Looks for a Fix*, INVESTOR’S BUS. DAILY, Sept. 29, 2008, at A9. For further information about the CRO industry, visit the Internet site of the Association of Clinical Research Organizations (ACRO). ASSOCIATION OF CLINICAL RESEARCH ORGANIZATIONS, <http://www.acrohealth.org/cro-market1.html> (last visited July 17, 2011) [hereinafter ACRO WEBSITE]. CROs generated \$20 billion in revenue in 2010 and, in 2008, conducted clinical

quently, the United States, the epicenter for prescription drug R&D,<sup>5</sup> has become a major exporter of human clinical trial research and an importer of resulting data.<sup>6</sup> Yet, even with this outsourcing and exporting trend, the current amount of clinical research occurring within the United States is unprecedented: In the first half of this decade alone, domestic clinical research increased nearly fifty percent.<sup>7</sup> Phase III trials, the final stage of clinical research before drug approval applications are submitted, have expanded to 20,000 subjects from just 3,000 five years ago, doubling their cost and surpassing \$100 million in expenditures.<sup>8</sup> According to the pharmaceutical industry, “[i]n 2009, America’s pharmaceutical research and biotechnology companies continued to make the world’s largest investment in pharmaceutical R&D, holding steady with \$65.3 billion spent on R&D, including \$45.8 billion by PhRMA members alone.”<sup>9</sup>

In spite of this tremendous investment in drug R&D, the United States approved just eighteen new drugs in 2007, a twenty-five year low; 2008 (twenty-four approvals) and 2009 (twenty-six approvals) were not much

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trials involving more than 2 million participants in 115 countries. *Id.*; see also Barbara J. Evans, *Seven Pillars of a New Evidentiary Paradigm: The Food, Drug, and Cosmetic Act Enters the Genomic Era*, 85 NOTRE DAME L. REV. 419, 424 (2010).

5. For information about the U.S. biopharmaceutical sector, visit the Internet sites of the United States-based pharmaceutical trade organization (PhRMA) and the biotechnology trade organization (BIO). PhRMA, <http://www.phrma.org> (last visited July 17, 2011); BIO: BIOTECHNOLOGY INDUSTRY ORGANIZATION, <http://www.bio.org> (last visited July 17, 2011). The United States has pursued global life-science leader status through aggressive technology transfer laws and policies that have integrated academia, industry, and government in biomedical research and development. See generally ROGER L. GEIGER, RESEARCH & RELEVANT KNOWLEDGE, AMERICAN RESEARCH UNIVERSITIES SINCE WORLD WAR II (2004); Michael J. Malinowski, A Discourse on the Public Nature of Research in Contemporary Life Science: A Law-Policy Proposal to Promote the Public Nature of Research in Contemporary Life Science, Keynote Address to Academia Sinica (Dec. 21, 2008), in BIENNIAL REV. L. SCI. & TECH. 2 (Wen-Tsong Chiou ed., 2010) [hereinafter Discourse on Public Nature]; Michael J. Malinowski & Radhika Rao, *Legal Limitations on Genetic Research and the Commercialization of Its Results*, 54 AM. J. COMP. LAW 45, 45 (2006); see also Owen C.B. Hughes, Alan L. Jakimo & Michael J. Malinowski, *United States Regulation of Stem Cell Research: Recasting Government’s Role and Questions to be Resolved*, 37 HOFSTRA L. REV. 383, 392-400 (2008). The United States invests tens of billions of dollars in basic research, transfers ownership of resulting inventions to universities and others conditioned on commercial application, and it has intensely done so for over two decades. See generally Discourse on Public Nature, *supra*; GEIGER, *supra*. For information about U.S. federal technology transfer law and policy, including background information, economic theory, enacting legislation, and technical requirements, see generally U.S. GEN. ACCOUNTING OFFICE, GAO/RCED-98-126, TECHNOLOGY TRANSFER: ADMINISTRATION OF THE BAYH-DOLE ACT BY RESEARCH UNIVERSITIES (1998) [hereinafter GAO TECHNOLOGY TRANSFER].

6. Nagano, *supra* note 4. For updated general information on the CRO industry, see ACRO WEBSITE, *supra* note 4.

7. The Center for Health & Pharmaceutical Law & Policy, CONFLICTS OF INTEREST IN CLINICAL TRIAL RECRUITMENT & ENROLLMENT: A CALL FOR INCREASED OVERSIGHT 5 (Nov. 2009) (Seton Hall Univ. Sch. of Law, White Paper) [hereinafter Center for Health White Paper].

8. See Nagano, *supra* note 4.

9. Letter from PhRMA’s President and CEO, in PROFILE: PHARMACEUTICAL INDUSTRY 5, 5 (2010), available at [http://www.phrma.org/sites/default/files/159/?profile\\_2010\\_final.pdf](http://www.phrma.org/sites/default/files/159/?profile_2010_final.pdf) (last visited Jan. 27, 2012); see also generally PhRMA, *supra* note 5.

better.<sup>10</sup> Recent market controversies in recent years surrounding products such as Vioxx (pain management), Avandia (treatment for Type-2 diabetes), and Accutane (acne medication) have raised concerns regarding the FDA's performance and trustworthiness in overseeing the nation's pharmaceutical market.<sup>11</sup> Congress recognized and addressed the problem with the Food and Drug Administration Amendments Act of 2007 (FDAAA).<sup>12</sup> This sweeping legislation augments premarket clinical studies, enhances the evidentiary standard, and imposes post-market communication through an Internet-based system.<sup>13</sup>

This Article questions the global "gold standard" for human clinical trial research and new drug approvals—namely, shared reliance through the ICH on statistical analysis to compile group means as the basis for market approval, known as group experimental design (GD).<sup>14</sup> The Article argues that heavy reliance on GD-generated clinical research data risks low predictive value about a prescription medicine's actual effect on individuals, including members of the groups under study, and continuation of the drug industries' fifteen-year slump in drug development.<sup>15</sup> In light of this

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10. Steven Burrill, *Steven Burrill Predicts Biotechnology's Fortunes for First-Half 2009*, PHARMA MARKETLETTER, Jan. 19, 2009, available at 2009 WLNR 7402398; Jared A. Favole, *FDA Approved More Drugs in 2008*, WALL ST. J., Jan. 2, 2009, at A9; Jenna Greene, *Has Obama Redirected the Regulatory System? After One Year, Some Agencies Can't Write Rules Fast Enough, While Others Sit and Wait*, NAT'L L. J., Jan. 18, 2010, at 11; Nagano, *supra* note 4 (noting 17 new U.S. drug approvals in 2007). PhRMA claims there were 34 new drug approvals in 2009—an inconsistency attributable to subjective determinations as to whether a drug is "new" or a modified version of one that already has reached the market. Industry Profile, *supra* note 9, at ii; see also Angus Robertson, *New Drug Approvals on Pace to Exceed 2008 Total*, RES. RECAP, June 9, 2009, available at 2009 WLNR 11054446.

11. See generally U.S. GOV'T ACCOUNTABILITY OFFICE, GAO-06-402, DRUG SAFETY: IMPROVEMENT NEEDED IN FDA'S POSTMARKET DECISION-MAKING AND OVERSIGHT PROCESS (2006) [hereinafter GAO DRUG SAFETY]; INSTITUTE OF MEDICINE, THE FUTURE OF DRUG SAFETY: ACTION STEPS FOR CONGRESS (2006) [hereinafter IOM DRUG SAFETY]; Thomas, *supra* note 2, at 365.

12. Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, 121 Stat. 823 (codified as amended in sections of 21 U.S.C.).

13. *Id.* For a thorough discussion of the FDAAA, see generally Evans, *supra* note 4; Barbara J. Evans, *Authority of the Food and Drug Administration to Require Data Access and Control Use Rights in the Sentinel Data Network*, 65 FOOD & DRUG L.J. 67 (2010).

14. See JANINE E. JANOSKY ET AL., SINGLE SUBJECT DESIGNS IN BIOMEDICINE 81 (2009); Gina Green, *On Single-Case and "N of 1" Research Designs for Evaluating Treatments for Autism Spectrum Disorders 5* (2009) (unpublished manuscript) (on file with authors). The technicalities of GD and single subject research design (SSRD) are addressed in depth, both individually and in a comparative fashion, in Michael J. Malinowski & Grant G. Gautreaux, *Drug Development—Stuck in a State of Puberty? Regulatory Reform of Human Clinical Research to Raise Responsiveness to the Reality of Human Variability*, ST. LOUIS L. REV. (forthcoming 2012) [hereinafter *Drug Development*], which presents an extensive science background discussion in Part II of that Article. This Article builds upon the science-based proposal to implement SSRD into U.S. Food and Drug Administration law and policy presented in *Drug Development* with a focus on changing the international norms for human clinical research in drug development. Specifically, it focuses on the ICH and the interplay between the European Medicines Agency (EMA), the FDA, and United States-based industry on the global level.

15. See generally Janosky, *supra* note 14; Green, *supra* note 14. See *infra* note 49 and the accompanying text (quoting Dr. Francis Collins regarding the industry's slump).

risk, the “gold standard” should be modified to reflect the increased precision associated with the “genomics revolution” in the drug development pipeline.<sup>16</sup>

Part I of the Article profiles the ICH and the globalization of human clinical research—primarily through proliferation of CROs with international networks in health care systems that provide access to patients. Emphasis is placed on the U.S. drug development industries’ trend towards outsourcing human clinical research (and toxicology studies) to CROs, and exporting research to jurisdictions outside of the United States.<sup>17</sup> This focus is reflective of the United States’ influence on global norms for human clinical research through the ICH, the sheer amount of research U.S. interests undertake, the direct international interface of the United States-based industries through their human clinical trial research activities, and their presence in the world’s major pharmaceutical markets.

Part II challenges reliance—by commercial drug developers, but also governments, regulators, and the health care establishment—on GD as the gold standard for human clinical trial research. This section introduces single subject research design (SSRD) as a methodology alternative or complement to GD for human clinical research in drug development.<sup>18</sup> Part III proposes law-policy reforms that modify the ICH standard for human clinical research to include SSRD. This proposal explores both European Union (EU) and United States-based approaches; the latter focus on commercial incentives and the United States’ influence on clinical trial standards through the ICH and its global market presence.

## I. The Globalization of Human Clinical Research

Significant progress has been made over the last two decades to harmonize science criteria among the world’s three largest pharmaceutical markets: the United States, Europe, and Japan.<sup>19</sup> The ICH gathers regulatory authorities and industry representatives from these markets to collec-

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For a full discussion of the slump in drug development, see *Drug Development*, *supra* note 14, and the citations therein.

16. Symposium, *Proceedings of “The Genomics Revolution? Science, Law, and Policy*, 66 *LA. L. REV.* 1, 2 (2005) [hereinafter *Genomics Revolution?*].

17. Nagano, *supra* note 4.

18. For a full discussion of SSRD and GD in the context of U.S. FDA law and policy, see generally *Drug Development*, *supra* note 14, at Parts II & IV; Janosky, *supra* note 14; Green, *supra* note 14; Robert H. Horner et al., *The Use of Single-Subject Research to Identify Evidence-Based Practice in Special Education*, 71 *EXCEPTIONAL CHILDREN* 165 (2005). See also J.M. JOHNSTON & H.S. PENNYPACKER, *Strategic Issues*, in *STRATEGIES AND TACTICS OF BEHAVIORAL RESEARCH* 296 (2d ed. 1993); J.M. JOHNSTON & H. S. PENNYPACKER, *Why Behavior Analysis is a Natural Science*, in *READINGS FOR STRATEGIES AND TACTICS OF BEHAVIORAL RESEARCH* 3 (2d ed. 1993); Mark Wolery & Susan R. Harris, *Interpreting Results of Single-Subject Research Designs*, 62 *PHYSICAL THERAPY* 445–52 (1982). Single subject studies and “N-of-1” (“number-of-one”) trials often are comingled, though most SSRD studies involve focused studies of and between multiple participants—not literally studies of single subjects.

19. ICH WEBSITE, *supra* note 2.

tively evaluate scientific and technical aspects of product registration.<sup>20</sup> Their primary objective is to reduce, and, ideally avoid, duplication of R&D for new medicines.<sup>21</sup> As a result, the ICH has developed shared scientific standards for clinical data and good clinical practice.<sup>22</sup> Notably, the ICH issued *E9 Statistical Principles for Clinical Trials* in 1998 to harmonize statistical methodologies used to support marketing applications.<sup>23</sup>

The government members have directly recognized ICH standards in their domestic law. The FDA, for example, conditions acceptance of data gathered outside the United States on compliance with U.S. regulations or ICH guidelines for good clinical practice.<sup>24</sup> More generally, ICH participants have extended their areas of consensus—incorporated into their domestic law-policy and industry operations—beyond the ICH markets through their biopharmaceutical R&D activities in the rest of the world.<sup>25</sup> Also, during the last few decades, science and its accompanying standards have transcended borders via global interface between scientific communities, industry interests, and governments engaged in the Human Genome Project and its progeny.<sup>26</sup>

More fundamentally, the sheer presence of U.S. interests in both biopharmaceutical R&D and the major markets for prescription medications has promoted the gold standard for human clinical trials throughout the world.<sup>27</sup> The U.S. government has distinguished itself through aggressive and direct investment in scientific research in an effort to raise the base of science—a practice inspired by the threat of annihilation by technology during WWII. The U.S. government has also distinguished itself through aggressive federal technology transfer laws, and policies that draw academia and industry together.<sup>28</sup> Indicative of its prominence, the United States invests more in scientific research than any counterpart, as do the American biopharmaceutical commercial interests.<sup>29</sup>

In order to access larger patient pools for clinical research, United States-based CROs are present in more than seventy countries, with substantial recent and ongoing expansion in Eastern Europe, India, Latin

20. See *id.*

21. See *supra* note 1 and accompanying text.

22. Michael J. Malinowski, *Ethics in a Global Pharmaceutical Environment*, 5 SANTA CLARA J. INT'L L. 57, 70-71 (2006).

23. See *E9 Guidance*, *supra* note 1, at 49,583-97.

24. ICH GUIDELINES, *supra* note 1.

25. See *generally* INTERNATIONAL FEDERATION OF PHARMACEUTICAL MANUFACTURERS & ASSOCIATIONS, *FOSTERING A POSITIVE DIALOGUE ON BEHALF OF THE RESEARCH-BASED PHARMACEUTICAL INDUSTRY* (2010).

26. See *generally* *Genomics Revolution?*, *supra* note 16.

27. See *generally* Industry Profile, *supra* note 9; BIOTECHNOLOGY INDUSTRY ORGANIZATION, *GUIDE TO BIOTECHNOLOGY* (2008), <http://www.bio.org/sites/default/?files/BiotechGuide2008.pdf>; Malinowski & Rao, *supra* note 5. The internet site for the U.S. biotechnology industrial organization is available at <http://www.bio.org>, and its European counterpart is available at <http://www.europabio.org>.

28. Discourse on Public Nature, *supra* note 5, at 2-24; see Geiger, *supra* note 5, at 7.

29. See *generally* Industry Profile, *supra* note 9; Center for Health White Paper, *supra* note 7, at 5; Discourse on Public Nature, *supra* note 5; GAO TECHNOLOGY TRANSFER, *supra* note 5.

America, Russia, and other emerging markets.<sup>30</sup> In addition to the receptiveness of health care systems, medical professionals, and patients to CRO recruitment efforts, these emerging markets offer “a large number of ‘treatment-naïve patients’ who aren’t taking other drugs and are thus the best candidates for trials.”<sup>31</sup>

## II. The Gold Science Standard and a Platinum Alternative<sup>32</sup>

The United States FDA did not require new drug sponsors to demonstrate efficacy until 1962, when the European Union (then the European Coal and Steel Community and the European Economic Community) did the same. This change was prompted by the thalidomide fiasco (a medication used for pregnancy-associated nausea that caused children to be born without limbs).<sup>33</sup> Since introducing the efficacy requirement, the core standard for market approval has been to beat a placebo or sugar pill. It is often enough for the drug to beat the placebo by one or two percentage points in a defined population, as long as it also makes a showing of tolerable safety.<sup>34</sup> Adverse drug reactions are accepted as an inevitable counterpart to prescription medications, and are a norm in the practice of medicine.<sup>35</sup>

To satisfy the efficacy standard, the FDA and new drug sponsors rely heavily upon GD as the preferred methodology for human clinical trials. GD refers to randomized studies in groups of people and statistical analysis to compile representative group means.<sup>36</sup> The reality of human variability suggests, however, that group averages may predict little about the actual impact of prescription medicines on specific individuals, including the studies’ participants who are the sources of the data used to generate the averages.<sup>37</sup> In other words, GD produces statistical abstracts that blanket over individual subjects, and, ultimately, any patient who receives the drug.

30. See generally *supra* note 4 and accompanying text.

31. See generally Nagano, *supra* note 4.

32. This section is drawn from the U.S. domestic law counterpart to this Article, Drug Development, *supra* note 14, at Part II.B.

33. Thomas, *supra* note 2, at 372 n.79, 373-74 nn.94-99; see *infra* notes 95-97 and accompanying text; see generally Michael J. Malinowski, *FDA Regulation of Biotechnology Products for Human Use*, in *ENCYCLOPEDIA OF ETHICAL, LEGAL AND POLICY ISSUES IN BIOTECHNOLOGY* 221 (Thomas J. Murray & Max Mehlman eds., 2002); David Classen, *Medication Safety: Moving from Illusion to Reality*, 289 *JAMA* 1154, 1154-56 (2003).

34. 21 C.F.R. § 314.126 (2011); *A PRACTICAL GUIDE TO FOOD AND DRUG LAW AND REGULATION* 25 (Kenneth R. Piña & Wayne L. Pines eds., 3d ed. 2002), available at <http://www.fda.org/pubs/previews/pdf/practical-guide.pdf>; Thomas, *supra* note 2.

35. Classen, *supra* note 33, at 1154-56; Jeffrey P. Braff et al., *Patient-Tailored Medicine, Part One: The Impact of Race and Genetics on Medicine*, 2 *J. HEALTH & LIFE SCI. L.* 1 (2008); Jeffrey P. Braff et al., *Patient-Tailored Medicine, Part Two: Personalized Medicine and the Legal Landscape*, 2 *J. HEALTH & LIFE SCI. L.* 1, 7 (2009).

36. See Drug Development, *supra* note 14, at Part II; see generally Janosky, *supra* note 14; Green, *supra* note 14.

37. See generally Janosky, *supra* note 14.



The crudeness of the GD standard in human clinical research for new drug R&D has affected the United States' broader law-policy regulatory scheme governing pharmaceutical use when delivering patient care. The U.S. commercial and privatized environment gives drug sponsors wide discretion over the studies they undertake and the product uses they seek in new drug applications.<sup>38</sup> The drug sponsors compile applications knowing that, once their products reach pharmacy shelves, the medical profession will embrace off-label uses that are often completely removed from the data before the FDA and the agency's actual approval for market access. The D.C. Circuit has observed that, "[N]either Congress nor the FDA has attempted to regulate the off-label use of drugs by doctors and consumers. A physician may prescribe a legal drug to serve any purpose that he or she deems appropriate, regardless of whether the drug has been approved for that use by the FDA."<sup>39</sup>

Often there are wide gaps between clinical data and clinical use of pharmaceuticals. For example, "[f]ew, if any, psychotropic drugs have been adequately evaluated in people with developmental disabilities, despite repeated calls for further research . . . . As in years past, further research is needed to produce data that will guide physicians in accurately matching drugs to patients."<sup>40</sup> Ultimately, the United States relies upon the medical profession to use patient-by-patient experiences over time to decipher prescription medications after they have been released on the market. In fact, according to a 2000 study published in the *American Journal of Economics and Sociology*, most cancer and AIDS patients receive drugs that are not FDA-certified for the prescribed use; and, in many fields of medicine, a majority of patients are prescribed at least one off-label drug.<sup>41</sup> This study also concluded that 80-90 percent of pediatric patient regimens involve at least one off-label prescription.<sup>42</sup>

Physician off-label discretion provides a powerful incentive for aggressive drug manufacturers to market their products to both health care providers and patients—the consumers in the U.S. system. These investments have proven to be effective and lucrative. Throughout much of the twentieth century and into the present one, pharmaceutical R&D has been *the* most profitable industry in the United States, and, in spite of its unprecedented investment in R&D, the pharmaceutical sector presently spends more on marketing than on R&D.<sup>43</sup>

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38. *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 349 (2001); *Washington Legal Found. v. Henney*, 202 F.3d 331, 333 (D.C. Cir. 2000); *Washington Legal Found. v. Friedman*, 13 F. Supp. 2d 51, 56 (D.D.C. 1998), *vacated in part on other grounds*, 202 F.3d 331 (D.C. Cir. 2000).

39. *See Henney*, 202 F.3d at 333; *see also Evans, supra* note 4, at 509-10.

40. Alan Poling, et al., *Pharmaceutical Interventions and Developmental Disabilities*, in *DEVELOPMENTAL DISABILITIES: ETIOLOGY, ASSESSMENT, INTERVENTION, AND INTEGRATION* 105, 119 (W. Larry Williams ed., 2004).

41. Daniel B. Klein & Alexander Tabarrok, *Do Off-Label Drug Practices Argue Against FDA Efficacy Requirements? A Critical Analysis of Physicians' Argumentation for Initial Efficacy*, 67 *AM. J. ECON. & SOC.* 743 (2008) (internal citations omitted).

42. *Id.* at 755.

43. MARCIA ANGELL, *THE TRUTH ABOUT DRUG COMPANIES* xv, 3, 11-12 (2004).

Experience illustrates the obvious danger of waiting to meaningfully understand prescription drugs' effect on individuals until after they are on the pharmacy shelves and patients are receiving physician care rather than volunteering for regulated studies. Even when marketed legally,<sup>44</sup> only one-third of prescription medicines act as expected when prescribed to patients, and according to the Institute of Medicine, there are approximately two million serious adverse drug reactions per year,<sup>45</sup> resulting in two million hospitalizations and 100,000 deaths annually.<sup>46</sup> While some of these adverse reactions derive from errors when prescribing and dispensing the medications, many of them are attributable to variations among individuals, such as how they metabolize the drugs.<sup>47</sup>

The opportunity costs to human health—lost opportunities for alternative treatment and investment in R&D and manufacturing resources for new drug efforts—are undefined. Market outcomes also suggest that drug development is suffering from the low R&D science standard. While an infusion of government and private investment has advanced genetic science beyond expectations, it has not produced a meaningful mass of new drugs in recent years: 2007 was the worst year for new drug approvals in a quarter of a century.<sup>48</sup> As observed by Dr. Francis Collins, Director of the National Institute of Health (NIH) and the head of the U.S. government's effort to map the human genome, "the drug industry's research productivity has been declining for 15 years, 'and it certainly doesn't show any signs of turning upward.'"<sup>49</sup> Concern and frustration have inspired the establishment of a new federal research center, under Dr. Collins' direction, to help the industry out of its slump.<sup>50</sup>

Experiences with Vioxx (a painkiller removed from the market after years of use due to an association with both heart attacks and strokes, and challenges to efficacy claims) and controversies involving drugs such as Avandia (a diabetes drug associated with increased rates of heart attack

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44. "In its 2006 policy guide, the FDA estimated there are up to several thousand drugs—including nearly 2% of all prescription drugs—marketed illegally without required FDA approval. These include compounds with unapproved active ingredients such as antihistamines, narcotics and sedatives." Harris Meyer, *Medicine: Costly Stamp of Approval*, L.A. TIMES, Jan. 18, 2010, at E3, available at 2010 WLNR 1055167.

45. Braff, *supra* note 35, at 9, 16–17.

46. B.S. Shastry, *Pharmacogenetics and the Concept of Individualized Medicine*, 6 PHARMACOGENOMICS J. 16, 16 (2006). For a discussion of the tremendous variability in the practice of medicine for the same diagnoses, see John Carey, *Medical Guesswork: From Heart Surgery to Prostate Care, The Health Industry Knows Little About Which Common Treatments Really Work*, 3989 BUS. WK. 72 (2006).

47. Petra A. Thürmann, *Prescribing Errors Resulting in Adverse Drug Events: How Can They Be Prevented?*, 5 EXPERT OPINION ON DRUG SAFETY 489, 489–93 (2006); Kathryn A. Phillips et al., *Potential Role of Pharmacogenomics in Reducing Adverse Drug Reactions: A Systematic Review*, 286 JAMA 2270, 2270–79 (2001).

48. See *supra* notes 10–13 and accompanying text; see generally Burrill, *supra* note 10.

49. Gardiner Harris, *New Federal Research Center Will Help Develop Medicines*, N.Y. TIMES, Jan. 23, 2011, at A1 (discussing the federal government's decision to launch a billion-dollar drug development center to help the industry create new pharmaceuticals and quoting Dr. Francis S. Collins, Director of the National Institute of Health).

50. *Id.*

and heart failure) raise serious questions about the reliability of FDA oversight.<sup>51</sup> The Government Accountability Office and Institute of Medicine have seriously questioned the FDA's regulatory performance after approving drugs which become available for use with follow-on study conditions that are not enforced.<sup>52</sup>

An area of concern is the FDA's execution of section 506B of the Food and Drug Administration Modernization Act (FDAMA)<sup>53</sup>—a provision that creates a presumption in favor of market approval with post-marketing study conditions, accompanied by FDA enforcement authority.<sup>54</sup> Although section 506B is consistent with the addition of efficiency, efficacy, and safety to the FDA's mission for review and approval of new drugs,<sup>55</sup> the agency has been lax in enforcing the post-marketing study conditions.<sup>56</sup> Congress responded with the sweeping FDAAA legislation, which culls more data during the clinical trial process using the familiar GD science standard.<sup>57</sup>

Given that the FDA is not executing its post-marketing responsibilities, focus must shift to the science standard for putting new drugs on the market. In this age of genetic precision in drug R&D, the GD gold standard must be revisited. Drug development should be aligned with the patient-centered focus of drug delivery in health care. It is unacceptable to rely so heavily on patient-physician experiences over extended periods of time, typically several years, to acquire meaningful understanding of prescription medications on pharmacy shelves that are relied upon to treat human ailments.<sup>58</sup> As recognized by Dr. Janosky, an expert in SSRD:

In a primary care setting, the patient generally exhibits symptoms and the physician follows evidence-based or appropriate steps to treat these symp-

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51. See generally Thomas, *supra* note 2. According to the editors of the *New England Journal of Medicine*, "with Vioxx, Merck and the FDA acted out of ruthless, short-sighted, and irresponsible self-interest." Richard Horton, Editorial, *Vioxx, the Implosion of Merck, and Aftershocks at the FDA*, 364 LANCET 1995, 1996 (2004).

52. See generally GAO Drug Safety, *supra* note 11; IOM Drug Safety, *supra* note 11.

53. 21 U.S.C. § 356b (2006).

54. Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, 111 Stat. 2296 (1997) (codified primarily in sections throughout 21 U.S.C., including §§ 352, 355, 356, 360aaa-1-3, 379r) [hereinafter FDAMA]. Section 506B of FDAMA, the provision that promotes this presumption in favor of market approval, is accompanied by FDA enforcement authority under 21 U.S.C. § 356b. See 21 U.S.C. § 356b; Thomas, *supra* note 2, at 367.

55. Malinowski, *supra* note 33.

56. U.S. GOV'T. ACCOUNTABILITY OFFICE, GAO-10-68, DRUG SAFETY: FDA HAS BEGUN EFFORTS TO ENHANCE POSTMARKET SAFETY, BUT ADDITIONAL ACTIONS ARE NEEDED (2009).

57. See *supra* notes 12-13 and accompanying text. The FDAAA methodology also includes gathering and disseminating information from the market via Sentinel, an expansive Internet-driven information system presently under construction. See generally Evans, *supra* note 4; Evans, *supra* note 13. For information about Sentinel, see generally FDA, *The Sentinel Initiative: An Update on FDA's Progress in Building a National Electronic System for Monitoring the Postmarket Safety of FDA-Approved Drugs and Other Medical Products* (July 2010), available at <http://www.fda.gov/downloads/Safety/FDAsSentinelInitiative/UCM233360.pdf> (last visited July 17, 2011).

58. Wylie Burke & Bruce M. Psaty, *Personalized Medicine in the Era of Genomics*, 298 JAMA 1682, 1682-84 (2007).

toms. The physician evaluates the patient's history signs, symptoms, medical test results, and examines the patient, and subsequently implements a treatment or intervention if warranted. . . . In primary care settings, standardized procedures are employed that include objective measurement of the outcomes, such as systolic blood pressure measurements. These design and intervention procedures are analogous to the standardized procedures used in single subject research designs, such as testing the effectiveness of a medication over a course of time.<sup>59</sup>

In fact, using GD to develop and approve new drugs may directly restrain the actual practice of medicine when used on-label. As explained by the renowned Dr. Jerome Groopman:

Clinical algorithms can be useful for run-of-the-mill diagnosis and treatment—distinguishing strep throat from viral pharyngitis, for example. But they quickly fall apart when a doctor needs to think outside their boxes, when symptoms are vague, or multiple and confusing, or when test results are inexact. In such cases—the kinds of cases where we most need a discerning doctor—algorithms discourage physicians from thinking independently and creatively. Instead of expanding a doctor's thinking, they can constrain it.<sup>60</sup>

For over half a century, science literature has discussed SSRD as an alternative natural science research methodology to GD.<sup>61</sup> SSRD draws much more data from individual subjects and works with the subjects' data directly, rather than through group statistics:

The core SSRD methodology is to repeat comparisons of control and treatment conditions with the same individual or staggered across similar individuals, graph the data on a subject-by-subject basis, and then analyze the resulting data. Human variability is accounted for in single subject research by manipulating environmental variables that occasion steady states of responding—rather than herding subjects through statistical analysis into what are declared to be steady states for the individual, but only actually represent the group averages.<sup>62</sup>

While a portfolio of disciplines, including behavior analysis, education, physical therapy, and occupational therapy, have developed SSRD over the years, biomedicine has largely ignored the methodology.<sup>63</sup> It has done so despite the fact that SSRD's focus on individuals would allow human clinical research to better approximate the practice of medicine: "To

59. JANOSKY, *supra* note 14, at 81.

60. JEROME GROOPMAN, *HOW DOCTORS THINK* 5 (2008).

61. *See generally* Janosky, *supra* note 14; *see also* Horner et al., *supra* note 18, at 165-79; J. M. JOHNSTON & H. S. PENNYPACKER, *Strategic Issues*, in *STRATEGIES AND TACTICS OF BEHAVIORAL RESEARCH* 296-309 (2d ed. 1993); J. M. JOHNSTON & H. S. PENNYPACKER, *Why Behavior Analysis is a Natural Science*, in *READINGS FOR STRATEGIES AND TACTICS OF BEHAVIORAL RESEARCH* 3-17 (2d Ed. 1993); John O. Cooper, Timothy E. Heron, & William L. Heward, *Multiple Baseline and Changing Criterion Designs*, in *APPLIED BEHAVIORAL ANALYSIS* 200-24 (2007); Mark Wolery & Susan R. Harris, *Interpreting Results of Single-Subject Research Designs*, 62 *PHYSICAL THERAPY* 445-52 (1982).

62. *Drug Development*, *supra* note 14, at 17 (manuscript draft).

63. JANOSKY, *supra* note 14, at 81; Poling, *supra* note 40, at 119 ("[T]hese methods have been used infrequently in clinical psychopharmacology.").

some extent, clinical medicine always has been tailored to the patient in that each physician-patient relationship is unique, and each clinical encounter represents the physician's attempt to provide the optimal care to the patient in the examining room, the emergency room, the hospital bed, and the intensive care unit.<sup>64</sup>

Responsible administration of medication in the delivery of care innately centers upon the individual. A doctor examines the actual effect that a prescription drug has on a patient by scrutinizing human-drug interactions and individual responsiveness. Consequently, the global gold standard for human clinical research in drug development, as recognized by the ICH, should be modified to include an SSRD component that better deals with the reality of human variability.

### III. A Law-Policy Proposal to Create a Standard Brighter than Gold

While immediate and direct change of the global GD standard for clinical research at the ICH level is needed, it is impracticable at this time. The world's dominant commercial interests comprise half of the ICH's sponsors, and more than half of its Steering Committee members.<sup>65</sup> Moreover, the ICH is a forum for consensus building on issues with enormous financial implications—nothing less than pharmaceutical R&D throughout the World's largest three markets. Accordingly, the very nature of the ICH is to respond to its members based upon their norms, practices, and priorities.<sup>66</sup> Therefore, because the ICH members have decades of experience using GD in clinical research and little exposure to SSRD,<sup>67</sup> the ICH, as a representative of their collective interests, is unlikely to voluntarily deviate from the familiar gold standard in human clinical research.<sup>68</sup> In fact, the ICH would probably even refuse to contemplate guidelines promoting SSRD inclusion without initiative from its members.

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64. Braff et al., *supra* note 35, at 9 (citing Burke & Psaty, *supra* note 58, at 1682-84).

65. The United States has been represented by both the FDA and PhRMA, Europe has been represented by the European Medicines Evaluation Agency (EMA) and the European Federation of Pharmaceutical Industries Associations (EFPIA), and Japan has been represented by the Ministry of Health, Labor and Welfare and the Japan Pharmaceutical Manufacturers Association (JPMA). In addition to the representatives of these six sponsors, the Steering Committee includes members of the International Federation of Pharmaceutical Manufacturers Associations (IFPMA) and observers from Health Canada, the World Health Organization, and Swissmedic, Swiss Agency for Therapeutic Products. Six conferences have been held, and the ICH7 Conference was scheduled to take place March 29-30, 2006, in Vienna, Austria, but was cancelled. For information about ICH, see generally *Steering Committee*, ICH, <http://www.ich.org/about/organisation-of-ich/steering.html> (last visited 16 October, 2011).

66. See *Vision*, ICH, <http://www.ich.org/about/vision.html> (last visited July 11, 2011) (placing emphasis on consensus building).

67. See *supra* notes 61-62 and accompanying text (noting the use of SSRD in many disciplines, but largely ignored by biomedicine).

68. John Barton, Keynote Address at the Santa Clara University School of Law Annual Biotechnology Conference: The Globalization of Pharmaceutical Development: Race, Markets and Ethics (Mar. 17, 2006).

The most pragmatic approach to modify the GD standard would be to effectuate change at the ICH government-participant level to develop biopharmaceutical R&D experience with SSRD. Viable options include initiating change at the European Union level, within individual EU member countries which could eventually influence the European Union, or in the United States. Arguably the ideal approach would combine all three.

#### A. Change at the European Union Level

Each of the ICH government participants could initiate modification of the GD standard. Among the three options (the United States, Japan, and the European Union), the European Union's government and medical community norms are the most consistent with the notion that SSRD would introduce—that heightened understanding of new biopharmaceuticals ought to be a prerequisite for market access.

In the European Union, product approval is not the equivalent of market access. Rather, product approval simply introduces an opportunity for drug sponsors to negotiate with government regulators about cost and whether to include the drug in the government's nationalized or socialized health care systems.<sup>69</sup> Moreover, physicians throughout the European Union are generally accustomed to open rationing and prescribing within the parameters of practice guidelines. EU physicians and patients are also exposed to less direct drug marketing than their U.S. counterparts, and they tend to be more cautious with new pharmaceuticals.<sup>70</sup> For example, in the United Kingdom, the label and marketing materials for new pharmaceuticals contain a black triangle symbol as a visual reminder that they have yet to be tried and tested through market use over time.<sup>71</sup> These differences make it probable that the World Medical Association (WMA)—the major international organization that represents physicians, works to ensure their independence, and promotes medical ethics—would be internally divided over a proposal to officially change the GD standard. This internal division could prevent the WMA from effectively opposing such a change at the EU and ICH levels.<sup>72</sup>

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69. Socialized medicine was actually introduced to fend off socialism. See generally Timothy Stoltzfus Jost, *Why Can't We Do What They Do? National Health Reform Abroad*, J. LAW, MED. & ETHICS 433, 433-41 (2004) [hereinafter *What They Do*]. Increasingly, patients are shouldering co-payments and turning to private insurance to supplement government health care coverage, but this is still a world away from the U.S. system that invites aggressive marketing of physicians and patients. See *id.*; see also TIMOTHY STOLTZFUS JOST, READINGS IN COMPARATIVE HEALTH LAW AND BIOETHICS (2d ed. 2007) [hereinafter READINGS]. For example, pharmaceutical coverage under the U.K.'s national system is means-tested. *What They Do*, *supra*, at 435. Ultimately, prescription medications often are administered through privately-owned pharmacies that work in conjunction with their health care systems, and there is an expanding secondary insurance private system in most markets, but it is supplemental. *Id.*

70. See sources cited *supra* note 69.

71. The Institute of Medicine recommended that the United States adopt the same in its report on the future of drug safety. IOM Drug Safety, *supra* note 11, at 5.3.

72. For information about the WMA, see generally WMA, <http://www.wma.net/en/10home> (last visited July 18, 2011). The WMA was established in 1947, in sync with the Nazi doctor trials at Nuremberg, "to ensure the independence of physicians, and to work

Despite the WMA's probable lack of opposition, any attempt to modify a systemic science standard for human clinical research within the European Union would trigger opposition from internal EU interests and external U.S. interests. Alternatively, these interests could be harnessed to realize the desired change, as addressed below.

## B. Change at the EU Member State Level

Efforts could be made to modify the GD standard within the European Union's member states in an attempt to motivate change within the ICH. Compared with the FDA, the European Union's pharmaceutical gatekeeper, the European Medicines Agency (EMA), wields far less power over its member states. First, the EMA's drug approval role is limited. The EMA permits a dual-approval process that, for non-biotech drugs, gives pharmaceutical companies the option of seeking member state approval and reciprocity. The system offers drug sponsors the choice between a centralized EMA process and a decentralized, member state alternative.<sup>73</sup> The EMA also outsources much of its work to national agencies.<sup>74</sup> This system results in national drug approval agencies competing for EMA centralized review opportunities, while also trying to attract drug sponsors to the individual member state review track. This competition among the national agencies "to win sufficient volume of work to enable them to retain a strong scientific and evaluation base which will then assist them in gaining further work,"<sup>75</sup> leads to practical and administrative issues. Notably, "[t]he E.U.'s dual route approval process does more than give the pharmaceutical companies two bites at the approval apple. The regulators essentially divide and conquer themselves."<sup>76</sup>

Ultimately, the EMA leaves enforcement to member states, and affords them considerable deference to control their health care systems.<sup>77</sup> In other words, the EMA makes recommendations to the member states, but pharmaceutical consumption and compliance depends on the member states and their choices.<sup>78</sup> It is true that "[t]he EMA is charged with biotechnology approvals. It is, however, but a 'quasi-regulatory body.' It has

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for the highest possible standards of ethical behaviour and care by physicians, at all times." *About the WMA*, WMA, <http://www.wma.net/en/60about> (last visited July 18, 2011). The organization actually is a confederation of professional associations that operates based upon consensus, and the AMA is a powerful member.

73. For general information about the EMA, see generally EUROPEAN MEDICINES AGENCY, <http://www.ema.europa.eu/ema> (last visited Mar. 10, 2011). All biotech drugs must go through the centralized process. See *Central Authorisation of Medicines*, EUROPEAN MEDICINES AGENCY, [http://www.ema.europa.eu/ema/index.jsp?curl=pages/?about\\_us/general/general\\_content\\_000109.jsp](http://www.ema.europa.eu/ema/index.jsp?curl=pages/?about_us/general/general_content_000109.jsp) (last visited Nov. 19, 2011).

74. *EU Member States*, EUROPEAN MEDICINES AGENCY, [http://www.ema.europa.eu/?ema/index.jsp?curl=pages/partners\\_and\\_networks/general/general\\_content\\_000219.jsp](http://www.ema.europa.eu/?ema/index.jsp?curl=pages/partners_and_networks/general/general_content_000219.jsp) (last visited Nov. 18, 2011).

75. Thomas, *supra* note 2, at 378.

76. *Id.* at 377 n.137. According to one commentator: "That companies have been selecting the decentralized approval route over the centralized route may suggest a race to the regulatory bottom." *Id.* at 378.

77. See generally READINGS, *supra* note 69, at 86-94.

78. Thomas, *supra* note 2, at 378.

exclusive authority over these decisions through the centralized process, but it does not have enforcement authority. Rather, it makes recommendations to the host nation of the pharmaceutical company at issue.”<sup>79</sup>

Most individual EU member states could adopt a modified clinical research policy, given that they avoid the multi-party and division-of-power government complications associated with the United States. As observed by Professor Jost, “in most European countries it is possible for ruling parties to enact and implement health reform legislation . . . . By contrast, the governing institutions of the U.S. were in fact designed to block radical change.”<sup>80</sup> Nevertheless, it is unlikely that individual EU member states could change ICH policy. In general, the member states compete at least as much as they collaborate on major economic issues and those affecting their national health care policies. Even if internal EU resistance could be overcome, any effort to change the global clinical research standard at the EU member state level would not stand up to U.S. interests given their influence over the ICH, the European Union, and its member states’ national agencies.

In addition to the resistance from U.S. interests, there would probably be internal EU resistance. While the U.S. government is arguably subjected (and receptive) to pharmaceutical lobbying on unmatched levels,<sup>81</sup> the European Union also is susceptible.<sup>82</sup> As stated by one commentator, “E.U. regulators are also not immune from outside influence. As in the U.S., pharmaceutical companies are seen as powerful lobbyists within the E.U.”<sup>83</sup> As with federal-state tension in the United States, the complications associated with EU member state pharmaceutical regulations invite both industry lobbying and gaming by drug sponsors.<sup>84</sup>

79. *Id.*

80. *What They Do*, *supra* note 69, at 437. The United States did enact the Patient Protection and Affordable Care Act of 2010 (PPACA), and health care reform, federal and state, is underway. See Patient Protection and Affordable Care Act of 2010, Pub. L. No. 111-148, 124 Stat. 119 (2010) as amended by the Health Care and Education Reconciliation Act of 2010, Pub. L. No. 111-152, 124 Stat. 1029 (2010). However, the government and public are grappling over its implementation, and PPACA is the target of both legal and financial policy challenges as the existing health care system slides into financial crisis. See generally *Health Reform: Prospering in a Post-Reform World* (Price-WaterhouseCoopers’s Health Research Inst., May, 2010).

81. “In the U. S., the political clout of the pharmaceutical companies is unparalleled. Indeed, the pharmaceutical industry has the largest lobbying organization in Washington.” Thomas, *supra* note 2, at 376.

82. The World Health Organization has recognized the same:

The World Health Organization, for example, has concluded that attaining pharmaceutical cost-containment in Europe “is likely to be a long and difficult process” because of “the lobbying power of the pharmaceutical industry.” The European Association of Hospital Pharmacists contends that it can attain its goals “through making contacts and lobbying at the European Commission, the Pharmaceutical Group of the European Union, the Industrial Pharmacists’ Group and the World Health Organisation’s Europharm Forum, among others.”

*Id.* at 376 nn.125-26.

83. *Id.* at 377 nn.132-33.

84. For a discussion of PPACA, the national health care legislation, see *supra* note 80. “Moreover, the very mix of multi-national and national regulatory structure itself,



### C. Change at the U.S. Level

In light of the potential for overwhelming resistance from U.S. interests to changing the ICH science standard for human clinical research at the EU and EU member state levels, any such attempts would need to address the U.S. interests head-on. This would require using both the FDA and Congress to insert a SSRD standard into industry practice. Such a change would not only temper U.S. interests in the European Union, but would also independently influence the ICH to modify its standard.<sup>85</sup>

Although changing U.S. industry practice would be difficult in light of the biopharmaceutical sector's immense lobbying of the U.S. government,<sup>86</sup> existing programs provide precedent for getting the desired clinical research done.<sup>87</sup> Moreover, given that the drug development industries have not been producing a meaningful number of innovative new drugs and, of those they have produced, several have proven to be serious disappointments, Congress has become dissatisfied and impatient with both the FDA and the drug development industries. Congress made this sentiment clear through enactment of the FDAAA, which increases the amount of information required during the drug approval process to break from the established practice of waiting until the delivery of care to gather this information.<sup>88</sup> The Obama Administration is also establishing a new "industry assistance" research center—headed by Dr. Francis Collins, Director of NIH and head of the U.S. government's effort to map the human genome—to help jumpstart the drug development industry.<sup>89</sup>

Due to the U.S. government's frustration with the drug development sector, it may be open to adoption of the SSRD standard. For example, the new "industry assistance" center's mission could be expanded to directly conduct SSRD studies, and to demonstrate their utility in drug development. Also, the U.S. government could introduce a separate program to directly promote SSRD, extending the accomplishments of the Human Genome Project into human health benefits by advancing drug development through SSRD improvements to clinical research. Besides the direct infusion of government resources to establish the utility of SSRD, FDA regulatory precedent could support desired clinical research methods in the context of drug development.<sup>90</sup> The timing for such indirect, regulatory methods is good; disappointing drug industry performance and ineffective regulation of the finance and oil industries have increased public and polit-

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which allows manufacturers to select the approval route that they find most expeditious, might best be characterized as 'establishing a level playing field for business in Europe and the maintenance of a strong industry.'" Thomas, *supra* note 2, at 377 n.136.

85. For a more extensive discussion of the U.S. system in this context, see generally *Drug Development*, *supra* note 14.

86. See *supra* note 81 and accompanying text.

87. See *infra* text accompanying notes 98-100.

88. See generally Evans, *supra* note 4; Evans, *supra* note 13; *Drug Development*, *supra* note 14.

89. See *supra* note 49.

90. See *infra* notes 99-102 (Best Pharmaceuticals for Children Act) and 103-104 (Orphan Drug Act) and accompanying text.

ical openness to regulation.<sup>91</sup>

The FDA must be careful, however, before promulgating regulations that demand drug sponsors to undertake specific clinical trials because such demands have been met by litigation challenges in the past. Specifically, using the regulatory process to attempt to impose commercial uses on new drug candidates or specific types of human clinical trials on drug developers would invite allegations of undue impediment on the discretion to practice medicine and the commercial freedoms embedded in the private market system. Additionally, it would invite challenges of agency overreaching in violation of the Administrative Procedure Act.<sup>92</sup>

A vivid illustration of the FDA's inability to demand specific research is the FDA's attempt to require pediatric studies prior to the Best Pharmaceuticals for Children Act (BPCA). This attempt prompted a successful legal challenge that struck down the FDA's Pediatric Rule and necessitated corrective legislation.<sup>93</sup> Former FDA Commissioner David Kessler, who ran the agency while FDAMA was being negotiated, has noted this limitation:

I need to acknowledge the limits of FDA's authority. It is our job to review drug applications for the indications suggested by the manufacturer. We do not have the authority to require manufacturers to seek approval for indications which they have not studied. Thus, as a matter of law, if an application contains indications only for adults, we're stuck.<sup>94</sup>

Subsequently, there have been many reminders that the agency may not interfere with the practice of medicine. For example, the House Report that accompanied FDAMA expressly states that the "FDA has no authority to regulate how physicians prescribe approved drugs in the context of their medical practice. Physicians prescribing off-label uses of approved drugs is not within the jurisdiction of the FDA."<sup>95</sup> In 2000, the Court of Appeals for the District of Columbia went even further when it determined that FDAMA provisions addressing manufacturer promotion of off-label uses imposed an undue burden on commercial free speech in violation of the First Amendment.<sup>96</sup>

In order to sidestep the issues that FDA *requirements* present, it would be more pragmatic to facilitate single subject studies in clinical research through commercial *incentives*. The FDA has attempted to facilitate pharmacogenomic studies (patient-specific studies based upon genetic var-

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91. See David Leonhardt, *Underestimating Risk: What the Oil Spill and the Financial Crisis Have in Common*, N.Y. TIMES, JUN 6, 2010, at MM13.

92. Ass'n of Am. Physicians & Surgeons, Inc. v. U.S. Food & Drug Admin., 226 F. Supp. 2d 204 (D.D.C. 2002).

93. See Best Pharmaceuticals for Children Act, Pub. L. No. 107-109, 115 Stat. 1408 (2002) [hereinafter BPCA] (codified as amended in sections throughout 21 U.S.C. and 42 U.S.C.).

94. David Kessler, Speech of FDA Commissioner to the American Academy of Pediatrics (Oct. 14, 1992), *quoted in* Ass'n of Am. Physicians & Surgeons, Inc. v. FDA, 226 F. Supp. 2d 204, 218 (D.D.C. 2002).

95. H.R. REP. NO. 105-310, at 60 (1997).

96. See *generally* Wash. Legal Found. v. Henney, 202 F.3d 331 (D.C. Cir. 2000).

iations, or alleles) through guidelines, but the effort has proven futile without tangible commercial incentives.<sup>97</sup> Through commercial incentives, the FDA could and should facilitate SSRD to make clinical research more representative of the delivery of health care, and bridge the two fields.<sup>98</sup>

The effectiveness of commercial incentives to encourage desired methods of clinical research has been demonstrated through the BPCA. This legislation reinstated the FDAMA voluntary program for pediatric testing with the incentive of six months of market exclusivity.<sup>99</sup> The BPCA then went further by empowering the FDA to step over manufacturer resistance and complete pediatric trials under the agency's oversight, either by using third parties through the NIH, or with funding from a federal trust.<sup>100</sup> The BPCA has been effective. As of March 2004, just two years after Congress enacted the legislation, pharmaceutical manufacturers had issued 346 requests to evaluate prescription drugs for pediatric use, 97 drugs had been granted six months of exclusivity, and new labels had been approved for 70.<sup>101</sup> By February 2008, 145 drugs had been granted pediatric exclusivity.<sup>102</sup>

Similarly, the United States has successfully incentivized the drug development industries to perform desired pharmaceutical R&D under the Orphan Drug Act (ODA). This Act creates a rewards-based program that makes it commercially viable to develop drugs for small groups of patients by providing tax incentives, a seven-year period of market exclusivity, and other benefits.<sup>103</sup> As a result, the desired research now is being accomplished—some 350 orphan drugs have been approved in the U.S. market alone, and the program has been replicated by other countries.<sup>104</sup>

The market performance of the United States-based drug development industries speaks for itself: a quarter-century downturn and a defined fifteen-year slump in new drug approvals, as well as many market disappointments despite enormous industries, vast government investment, and

97. See *Genomics Revolution?*, *supra* note 16, at 93; see generally FOOD AND DRUG ADMIN., U.S. DEPT. OF HEALTH, GUIDANCE FOR INDUSTRY: PHARMACOGENOMIC DATA SUBMISSIONS (2005), available at <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126957.pdf>; 21 C.F.R. § 58, ch. 1, Pts. 300-69 (2010).

98. See generally *Drug Development*, *supra* note 14.

99. 42 U.S.C. § 284m(b), (c)(7) (2006).

100. *Id.*

101. Leslie Kushner, *Incentivizing Postmarketing Pharmaceutical Product Safety Testing with Extension of Exclusivity Periods*, 19 FORDHAM INTELL. PROP. MEDIA & ENT. L.J. 519, 547-48 (2009); see Rosemary Roberts, <http://www.fda.gov/cder/pediatric/?presentation/FDAMA-FDA%20Persp-Roberts2004/sld008.htm> (last visited Oct. 30, 2008) (on file with author).

102. FOOD AND DRUG ADMIN., *Drugs to Which FDA has Granted Pediatric Exclusivity for Pediatric Studies under Section 505A of the Federal Food, Drug, and Cosmetic Act*, available at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm050005.htm> (last visited Nov. 18, 2011).

103. See Orphan Drug Act, Pub. L. No. 94-414 § 526(a)(2), 96 Stat. 2049 (codified as amended at 21 U.S.C. § 360bb) (2000); Mark D. Shtilerman, *Pharmaceutical Inventions: A Proposal for Risk-Sensitive Rewards*, 46 IDEA 337, 337 (2006).

104. 2010 Report, PHRMA, <http://www.phrma.org/annual-reports/2010> (last visited Mar. 5, 2010).

cutting-edge enabling technology associated with genomic science.<sup>105</sup> To help solve this problem, the United States could and should enact legislation to commercially incentivize a shift from the GD standard to one that promotes SSRD. One option is direct government funding of SSRD studies, possibly by using the new “industry assistance” center created by President Obama. Another option is indirect government regulation that provides commercial incentives, similar to the BPCA and ODA, to engage in SSRD studies.

If SSRD succeeds in lifting drug development in the United States out of its present doldrums, it could create a “race to the top” among drug makers, which would lessen the overwhelming resistance from U.S. interests to similar change in the European Union and its member nations. This increased acceptance by drug development industries would then pressure the ICH, as a representative of its members’ collective interests, to modify GD as its gold standard. By incorporating SSRD, drug development would shift its focus to the reality of specificity associated with the genetic science that increasingly dominates the drug development pipeline, and would move drug development closer to the reality of the practice of medicine.

## Conclusion

Pharmaceutical R&D is an increasingly global endeavor, with considerable human health and economic implications.<sup>106</sup> The United States, European Union, and Japan have attempted to coordinate market access through ICH standard sharing that promotes the acceptance of clinical research data among the world’s three largest drug markets, thereby eliminating duplication and waste.<sup>107</sup> A danger of the ICH, with group decision making by representatives from three governments and industry representatives from several world markets, is its susceptibility to excessive industry influence and the entrenchment of standards that need modification.<sup>108</sup>

This Article and its domestic FDA law-policy counterpart<sup>109</sup> have asserted that the current shared global standard for human clinical research, GD, is antiquated and should be modified with an SSRD component. The underlying problem is that GD is not responsive enough to the reality of human variability, which is innate to the practice of medicine, or to genetics science, which increasingly dominates drug development.<sup>110</sup>

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105. See *supra* notes 49–50 and accompanying text.

106. See *supra* notes 4–6 (global clinical research through CROs), 24–26 (ICH), 30–31 (CROs global presence) and accompanying text.

107. See, e.g., E9 Guidance, *supra* note 1; see generally *supra* notes 1–3 and accompanying text; ICH WEBSITE, *supra* note 1. The United States is the largest market, followed by Europe. See Thomas, *supra* note 2, at 375.

108. The Steering Committee is dominated by industry representatives. See *supra* note 65 and accompanying text (identifying the ICH composition).

109. See generally *Drug Development*, *supra* note 14.

110. See *supra* notes 36–37 (GD and human variability), 61–64 (clinical research and the individualized nature of medicine) and accompanying text; see generally *Drug Development*, *supra* note 14.

Also, the GD approach places too much reliance on the medical profession working with patients over time. It relies on information gathered outside of the human clinical research context to fully establish clinical care understanding—a fact recognized by the U.S. Congress through the FDAAA.<sup>111</sup>

Because drug developers are relying on this antiquated standard, the biopharmaceutical sectors are in a fifteen-year slump in new drug approvals, and of those that have reached the market, many continue to cause millions of adverse events annually in the United States alone.<sup>112</sup> This Article argues that the basic science standard for human clinical research in pharmaceutical R&D needs to be modified to reflect the present and future—an SSRD component must be added to human clinical research. Doing so would not only shift the focus of clinical trials from group averages to a specific individual focus, bringing it in line with the actual practice of medicine, but would also reap the benefits of the genomics revolution.

The ICH's reluctance to change a scientific standard as rooted as GD is expected, given that the ICH is representative of its members' collective interest, and that these members depend on human clinical research for drug development.<sup>113</sup> Therefore, this Article has probed law-policy strategies at the ICH member level, including efforts focused at the European Union, its member states, and the United States. The Article has shown that, while the European Union's government and medical community norms are more consistent with SSRD, the influence from U.S. interests is likely to overwhelm any modification to the GD standard.<sup>114</sup>

This Article's ultimate proposal is that the United States should commercially incentivize the drug development industries to infuse an SSRD standard into their clinical research through direct government funding, indirect government regulation, or a combination of the two approaches. Doing so would lessen the resistance from U.S. interests and could encourage a similar shift in the European Union. As SSRD gains popularity, it would pressure the ICH to modify its GD gold standard to include a SSRD component, which could lead to a "race to the top" among drug manufacturers that would both break the slump in new drug approvals and align human clinical research with the practice of medicine.

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111. See *supra* notes 12-13 and accompanying text.

112. See *supra* notes 44-47 and accompanying text (adverse events and associated deaths) as well as notes 49-50 and accompanying text (15-year slump in drug approvals).

113. See *supra* notes 67-68 and accompanying text.

114. See *supra* note 85 and accompanying text.