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## Drug Development--Stuck in a State of Puberty?: Regulatory Reform of Human Clinical Research to Raise Responsiveness to the Reality of Human Variability

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Article

**\*363 DRUG DEVELOPMENT--STUCK IN A STATE OF PUBERTY?: REGULATORY REFORM OF HUMAN CLINICAL RESEARCH TO RAISE RESPONSIVENESS TO THE REALITY OF HUMAN VARIABILITY**

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Abstract

Scathing critiques of the Food and Drug Administration's ("FDA") performance by the Government Accountability Office and Institutes of Medicine, a plummet in innovative new drug approvals in spite of significant annual investment increases in biopharmaceutical research and development ("R&D"), and market controversies such as the painkiller Vioxx and the diabetes drug Avandia (both associated with significantly escalated risks of heart attacks and strokes) have raised doubts about the sufficiency of FDA \*364 regulation. This Article questions how prescription medicines reach the market and proposes law-policy reforms to enhance the FDA's science standard for human clinical trials and new drug approvals. The core message is that relying too heavily on clinical research data generated through the global "gold standard" of group experimental design--reliance on statistical analysis to compile and compare group averages--risks predicting little about the actual impact of prescription medicines on individuals, including members of the groups under study. This Article introduces a law-policy methodology based upon commercial incentives and intervention by Congress and the FDA to raise the science standard for human clinical research, and to make drug development more closely parallel the reality of drug delivery in the practice of medicine. The objectives of this proposal are to promote several pressing needs: maximize drug performance and minimize adverse events; end the pattern of putting new prescription medications on the market with too much dependence on the medical profession to introduce meaningful clinical understanding of drugs through patient use over time; improve biopharmaceutical R&D decision making; align the regulatory standard with the infusion of added precision associated with contemporary genetics-based R&D; and realize more sound scientific information directly through the

regulatory process to support the integrity of science in an age of academia-industry integration, aggressive commercialization, secrecy in science, and constantly, rapidly evolving technology.

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\*366 “2007 was the single worst year for new drug approvals in a quarter century and 2008 proved to be only slightly better.” [FN1]

“[T]he drug industry's research productivity has been declining for 15 years, ‘and it certainly doesn't show any signs of turning upward’ . . . .” [FN2]

“At present, our best advice for anyone concerned with the pharmaceutical treatment of behavior disorders in people with developmental disabilities is simple: Be skeptical and collect data.”

## Introduction

“Emma will never speak” was the conclusion of health care professionals when she was assessed for significant learning disabilities at the age of three. [FN4] Confirming what her parents had suspected and feared for much of her life, these health care professionals diagnosed Emma with an autism spectrum disorder. [FN5] Autism or not, Emma's parents did not accept the notion that their \*367 daughter would never speak, and especially the prognosis that nothing could be done to help her. They researched non-stop and exploited every resource to find appropriate educational support. Their efforts led to entering Emma into a program staffed by teachers focusing on her particular situation and taking moment-to-moment data on her responses, graphing and analyzing even minute components of her day. Teachers, working in close collaboration and constantly comparing and analyzing data, used the detailed information drawn from Emma and several other students clinically very similar to her to generate, implement, and test--individually and collectively--a litany of highly individualized interventions in an ongoing manner. Within a little more than one year, Emma acquired some functional speech, demonstrated learning at increasingly higher rates, showed IQ score improvements, and was successfully entered into a program that mainstreamed her with children developing according to “typical” indicators. The interventions--both successful and unsuccessful-- and accompanying, detailed data were derived from the tactics and strategies in the applied behavioral literature. Most of these interventions became the subject of a series of publications in the science literature to the benefit of other teachers, children, and the field in general.

Emma's story illustrates the cumulative effect yielded from single subject research design (“SSRD”), which entails a systematic implementation of the scientific method to analyze and treat behavioral problems. [FN6] SSRD, a natural science methodology for human clinical research, developed in practice and has been addressed in literature for over a half a century in disciplines such as behavior analysis, education, physical therapy, and occupational therapy. [FN7] \*368 With SSRD, evidence-based practices are identified vis-à-vis replication rather than the aggregate of results en masse. SSRD is an alternative to group experimental design (“GD”), the global “gold standard” for human clinical trial research in drug development. [FN8] GD is based in randomized, parallel, group trials. [FN9] While GD typically focuses on ascertaining statistically significant variations based upon group averages, [FN10] the core SSRD methodology is to repeat comparisons of control and treatment conditions with the same \*369 individual or staggered across similar individuals, graph the data on a subject-by-subject basis, and analyze the results. [FN11] Thus, the individual serves as her own control while the variables interacting between the individual and the environment are isolated. Such a finely grained approach enables the researcher to obtain valuable information about both the individual and the intervention, and more carefully police threatening complications. This research approach has not been utilized in drug development: “Although there is a long tradition of employing single subject designs in social science research, these designs have only recently been utilized in biomedicine.” [FN12]

This Article proposes law-policy reform of human clinical trials in drug development to promote the use of SSRD. A primary, overarching goal is to advance the transition from traditional pharmaceutical R&D, with its focus on taking away symptoms, to actually treating the causes of disease--at the cellular, genetic, and molecular levels. [FN13] Specifically, the Article challenges \*370 the FDA's extensive reliance on the GD model, which has governed clinical research since not too long after enactment of the Food, Drug and Cosmetic Act in 1938, [FN14] and suggests law-policy reforms to increase SSRD studies in drug development. A major premise is that regulation of human clinical trials should be responsive to the governing science, and SSRD emphasizes the reality of human variability [FN15] in a manner in sync with contemporary genetic science and the actual practice of medicine. [FN16] The core message is that relying on data generated through GD alone--again, group averages compiled through statistical analysis to test hypotheses--risks predicting little about the actual impact of prescription medicines on individual patients at the detriment of ongoing and future drug development, to the loss of multiple tens of millions of living patients waiting for treatments, who are suffering from ongoing, seriously debilitating, and even life-threatening human health ailments. [FN17] Such \*371 a reliance on this type of analysis may conceivably mask potentially effective treatments for individuals and life-threatening complications for others.

A major focus of discussion is the nexus between the regulation of drug development and the delivery of health care. Under the present law-policy scheme, drug review is too lenient, [FN18] practical yet sophisticated understanding of new pharmaceuticals is too limited, and market approval invites excessive off-label use--an approach that muddles clinical care with clinical research excessively, and exacerbates the unpredictability of prescription medications. [FN19] \*372 Ultimately, the medical profession exercises expansive prescription discretion, on and off FDA-approved labels, to sort through the actual safety, efficacy, and peculiarities of a drug patient-by-patient, and over time--typically years--after the drug is on the market. [FN20] As documented in one empirical study, "Off-label prescribing is very common in all areas of medicine. It is not uncommon for a drug to be prescribed more often off-label than on-label. . . . Indeed, 80 percent to 90 percent of pediatric patient regimens involve at least one off-label prescription." [FN21] Ironically, off-label usage has been common practice for individuals with developmental disabilities and autism, while some physicians do not always recognize applied behavior analysis as a validated treatment for autism due to the apparent dearth of large scale GD studies. [FN22]

Congress has recognized and addressed the problem through sweeping legislation known as the Food and Drug Administration Amendments Act of 2007 ("FDAAA"). [FN23] The methodology of FDAAA is to "augment premarket clinical studies" and try to cull more from resulting data "with new sources of evidence about the risks and benefits of drugs," but the Act does not change \*373 reliance on GD as the gold standard in drug development. [FN24] Rather, the core methodology of FDAAA is to do more with GD--in essence, to rely on it more. [FN25] Continued over-reliance on GD in human clinical studies coupled with extensive medical community discretion to essentially experiment on patients without systematically contributing to the research base--as opposed to clinical researchers experimenting on research subjects under human subject protections and direct FDA oversight--threatens to perpetuate a

crude working standard for prescription medications as they enter the market and for years thereafter. This regulatory approach is increasingly unacceptable in an age of genetic science. [FN26]

This Article begins by profiling GD in human clinical trials--again, the so-called gold standard and the cornerstone of the law-policy rubric governing market approval for human medicinal products. [FN27] Tremendous reliance on GD has been reinforced globally through the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use ("ICH") standard sharing. [FN28] Part I then introduces SSRD in an interdisciplinary, comparative manner through discussion that draws from a debate over GD and SSRD in human clinical studies developed in another health care context--the field of applied behavior analysis ("ABA"). [FN29] Specifically, the Comprehensive Application of Behavior Analysis to Schooling Program ("CABAS®") at Columbia University's Teachers College has utilized SSRD in research with and treatment of children with behavioral conditions and often severe learning disabilities, many labeled "autistic," and, \*374 more recently, neuro-typical children. [FN30] This is a highly protected group under the regulations to protect human subjects [FN31]--one that has been too often overlooked and avoided in clinical research for drug development and yet routinely prescribed medications that reach the market. [FN32] CABAS®, with a legacy of three decades of research and an international network of schools and graduates working in the field, has challenged the preexisting norms of heavy reliance on GD in clinical research and generated significant research accomplishments and documented treatment interventions. [FN33] In addition to the shared context of clinical research, treatment for patients with developmental disabilities depends heavily--arguably, often too heavily-- on utilization of prescription medicines made available through the drug development process without data sufficient for physicians to match drugs and patients. [FN34] These practices, in addition to raising cautionary concerns regarding unknown side effects, may also lead to an unsubstantiated yet alluring false efficacy.

Part II frames ongoing disappointments and frustrations with contemporary drug development and challenges the entrenched reliance on GD. Specifically, this Part questions continued dependence upon mathematical abstracts that, although representative of the group collectively, may say nothing decisive about members of the group individually, let alone broad populations of patients with health care needs outside the group. The discussion concludes that the core regulatory process to put drugs on the market lingers from the past and is disconnected from the patient-centered nature of the practice of medicine and the science disciplines that dominate today's innovative biopharmaceutical R&D. Part III proposes a regulatory overhaul of clinical research to modify the gold standard through utilization of SSRD. This proposal draws from past efforts by Congress and the FDA to shape clinical trial research through both direct mandates and commercial incentives, \*375 including the Best Pharmaceuticals for Children Act ("BPCA") [FN35] and the Orphan Drug Act ("ODA"). [FN36]

## I. The "Gold Standard" in Human Clinical Research and the SSRD Alternative

The following discussion summarizes the evolution of GD as the gold standard for clinical research and drug approval with a focus on the accompanying law-policy rubric that promotes it. [FN37] The discussion then profiles SSRD as an alternative natural science research methodology for human clinical research that, although increasingly recognized in biomedicine in recent years, remains highly underutilized in biopharmaceutical R&D. [FN38]

#### A. The Science and Law-Policy Rubric for Human Clinical Research

The law-policy surrounding human clinical trials reflects the regulatory role the FDA has evolved into during the decades after enactment of the Food, Drug, and Cosmetic Act of 1938 (“FDCA”). [FN39] The FDCA bestowed the Agency with the powers to assume a market gatekeeper role--the authority to examine, question, and evaluate the clinical utility of drugs. [FN40] Still, prior to 1970, the Agency made law primarily by pursuing judicial enforcement of statutory standards. [FN41] Subsequently, the Agency has shifted in the direction of an administrative law-policy approach--exercising its capacity as product reviewer and rule-maker--and has raised the burden on drug sponsors to earn market approval. As observed by authors Hutt, Merrill, and Grossman, “Faced \*376 with increasingly complex substantive issues and a growing number of firms making regulated products, FDA turned toward rulemaking as the principal technique for defining legal requirements. The agency attempted to resolve most of the major issues it confronted through administrative, rather than court, action.” [FN42] The FDA, as product reviewer and market gatekeeper, has been responsive to clinical trial data of effectiveness generated through implementation of the GD gold standard--randomized, parallel, group clinical trial designs. [FN43] The standard has been adopted globally, as recognized by the ICH in E9 Statistical Principles for Clinical Trials. The ICH issued E9 in 1998 to harmonize statistical methodologies used to support marketing applications. [FN44] The ICH serves as an advisory body for drug harmonization for the European Union (“EU”) through the European Medicines Agency (“EMA”), the United States through the FDA, and Japan through the Ministry of Health, Labor, and Welfare. [FN45] In 2008, the ICH developed technical requirements for registration of pharmaceuticals for human use. [FN46] The requirements defined key terms in the discipline of pharmacogenomics, including pharmacogenetics, genomic biomarkers, and genomic data, and provided sample drug coding categories. [FN47] The intent was “to develop \*377 harmonized approaches to drug regulation” and “to ensure that consistent definitions of terminology are being applied across all constituents of the [ICH],” as well as the “integration of the discipline of pharmacogenomics [(“PG”)] and pharmacogenetics into the global drug development and approval processes.” [FN48] In 2010, the ICH developed requirements for the context, structure, and format of voluntary biomarker submissions from PG research in order to create a “harmonized recommended structure for biomarker qualification” that will allow for consistency of applications and will “facilitate discussions with and among regulatory authorities.” [FN49] Between the three regulatory entities enveloped in the ICH, all three adhere to these standards, but at this point no standards have been developed to integrate PG into mainstream healthcare.

The resulting quid pro quo for market access is data generated through GD in four phases (sometimes classified as five) of clinical trials. [FN50] Phase I trials generally are conducted in tens of healthy volunteers for up to a month with the objective of making the transition from animal to human

participants through research on toxicity and a showing of safety. [FN51] Minimum doses are administered, and the healthy status of participants enhances the transparency of their impact. [FN52] With a focus on safety, the core objective of these trials is to assess the metabolic and pharmacological actions of the drug candidate in \*378 humans, and to identify side effects while increasing doses. [FN53] Phase I trials also may garner early evidence of effectiveness. [FN54] Phase II trials involve hundreds of participants drawn from the target disease group and span several months. [FN55] The objectives are to study the effectiveness of the new treatment, to determine short-term side effects and overall risks associated with the drug, and to develop advanced dosage criteria. [FN56] Phase III typically encompasses thousands of disease group participants at multiple sites with the goals of balancing safety and efficacy, to refine dosage, and establish overall effectiveness against a placebo (sugar pill) or other control. [FN57]

The data generated in Phase III shapes applications for market access. The baseline standard for market approval is to outperform a placebo on efficacy, perhaps just by a percentage point or two, with a showing of tolerable safety in a defined population. [FN58] Once biopharmaceuticals reach the market, the medical community has broad discretion to use them off-label--and does so aggressively. [FN59] The FDA continues to regulate pharmaceuticals post-market approval through Phase IV follow-on trials that probe lingering questions and strive to perfect clinical use, that is, to develop additional details about the product's safety and efficacy. [FN60] Congress has attempted to shift traditional \*379 Phase IV trials into premarket studies through the FDAAA. [FN61] Phase IV studies have been largely observational and centered on post-marketing surveillance to detect and define previously unknown or inadequately quantified adverse reactions and related risk factors. [FN62] In recent years, these studies often have distinguished defined demographic groups that may have been overlooked as a focus point during the trials that put the drugs on the market. [FN63] Areas of inquiry may involve formulation evaluations, dosages, the durations of treatment, and interactions with other medications. [FN64]

A major trend since implementation of the Food and Drug Administration Modernization Act of 1997 ("FDAMA") has been to err in favor of putting new drugs on the market on a watch-and-see basis to introduce access for patients in need, albeit conditioned with follow-on studies--often referred to as 506B studies. [FN65] This approach is consistent with expansion of the FDA's mission under FDAMA to include efficiency, along with efficacy and safety, for new drug approvals. [FN66] Unfortunately, the FDA has been lax in enforcing these post-market study conditions. [FN67]

\*380 FDA regulations and standards for clinical trial study design distinguish exploratory trials from confirmatory trials and hold the former to more rigid standards. [FN68] With the most common study design, parallel group experimental design, participants are randomized to one or more trial arms, and each arm is allocated a different treatment. [FN69] Ideally for the purposes of generating and collecting data both for safety and efficacy, GD comparisons are drawn between a group of participants taking the drug candidate and another administered a placebo to show statistically significant differences between group mean scores. [FN70] Double-blinding (neither the administering physician nor the participants know who actually is receiving the drug candidate) is used to check the risk of bias. [FN71] However, in practice, it tends to be much more complicated to incorporate participants' access to existing treatments into the studies. Research subjects are administered the drug candidate coupled with an



existing standard-of-care treatment. [FN72] Comparisons are made with groups \*381 given the standard treatment alone or, where there are multiple treatment options, the drug candidate with varied couplings. [FN73]

Since the introduction of the Prescription Drug User Fee Act in 1992 (“PDUFA”), the FDA has been granting accelerated approval of novel drugs based upon surrogate endpoints--laboratory measures that suggest improvements in patient health rather than factual documentation of actual impact given a contained timeframe--in accordance with formal clinical standards, meaning patient health improvements. [FN74] Inferences about the drug candidates are based on statistical comparisons of group mean scores. [FN75] The ultimate compilation is a statistical common denominator across the full target disease population.

A major limitation in GD for drug development is that human variability among study participants may prove significantly more substantial than anticipated even though, symptomatically, the subjects appear to share what has been classified a disease. [FN76] The mathematical abstract derived from the population may predict nothing for any individual participant. As explained by Professor Janosky,

[P]atients are unique and may not respond similarly to various treatments, and in those instances a randomized clinical trial design may be inappropriate. \*382 Guidelines are established from the averaged study findings, which may not necessarily be applicable when evaluating suitable treatment options for individuals. Specifically, patients treated in primary care settings may differ clinically from patients in the clinical trial, the patient diversity in the clinical trial may not generalize to certain patient populations, and the stringent trial criteria for accepting participants may not accurately reflect general patient populations. [FN77]

The effort to account for human variability and to generate a meaningful predictor of drug performance through GD, to the extent that is possible, demands thousands of participants at multiple locations--a need that has increased substantially over the last decade and pushed drug sponsors to outsource both toxicology studies and human clinical trials to contract research organizations (“CRO”). [FN78] “In the past, a single phase three trial might have needed 3,000 patients and cost between \$10 million and \$20 million. Today, the same kind of study would take 20,000 patients and cost \$50 million to \$100 million . . .” [FN79] While the trend is expansion of clinical trial recruitment outside of the U.S. borders, [FN80] “[t]he number of clinical trials in the United States has climbed dramatically in recent years. Between 2000 and 2006, \*383 clinical trials increased from 40,000 to 59,000--a nearly 50 percent jump.” [FN81] Though industry is spending unprecedented amounts on clinical research and conducting more and larger clinical trials, the sobering outcome is a steep drop in innovative new drug approvals in recent years. [FN82]

Congress has recognized and responded to the drug development dilemma by forcing more of GD through the FDAAA and culling more data around it rather than questioning the methodology. [FN83] The current administration is concerned enough to introduce a billion-dollar center, funded in a time of economic trouble, to infuse government-performed research assistance in order to help industry put more new drugs on pharmacy shelves. [FN84]

## B. The Advent and Evolution of SSRD

SSRD is a natural science research methodology developed in practice and addressed in literature for over a half a century in disciplines such as behavior analysis, education, physical therapy, and occupational therapy. [FN85] “Although there is a long tradition of employing single subject designs in social science research, these designs have only recently been utilized in biomedicine,” [FN86] and “these methods have been used infrequently in clinical psychopharmacology.” [FN87] However, the cross-discipline popularity of SSRD is on the rise: “In recent literature, it appears these designs are receiving more recognition, as they are being increasingly employed in research across disciplines.” [FN88]

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. [FN89]

\*384 Single-case design experiments to evaluate treatment effects involve directly observing and measuring one or more specific behaviors of an individual repeatedly for a period of time while a particular treatment is not in place (the control or baseline condition), and while it is (the experimental or treatment condition). . . . Comparisons of control and treatment conditions are repeated, or replicated, with the same individual and/or with other similar individuals. [FN90]

Human variability is accounted for in single subject research by manipulating environmental variables that occasion steady states of responding--rather using statistical analysis to herd subjects into what are declared to be steady states for the individual, but actually represent only group averages. Specifically,

In applied single-case studies, the interest is not in statistically significant differences between group mean scores but in clinically and educationally important improvements in individual behavior in comparison to baseline. In many behavior analytic studies, those changes--that is, differences in data from the control and treatment conditions--far exceed what is required for statistical significance. Individual differences in responses to treatment and variability in behavior are not viewed as “noise” to be wiped out mathematically, but as natural features of behavior to be studied further so they can be better understood. Replication, which is an essential ingredient of science, is built into single-case designs. . . . The evidence for those conclusions comes from conditions where the treatment and other variables are tightly controlled and the effects of the treatment on behavior are observed directly, rather than from statistical transformations of numbers that do not represent actual behavior. [FN91]

The SSRD and GD methodologies for responding to variability in outcomes are fundamentally different. [FN92] In GD, researchers typically use large samples to average out differences in outcomes, while SSRD researchers attempt to bring outcome differences under experimental control--in other words, statistical control over error through large samples under GD, versus experimental control to reduce error with a heightened focus on individual subject responses under SSRD. [FN93] As pointed out by Professor Janosky,

[The GD] strategy is problematic for two reasons: (1) statistical power and sample size are related, with larger samples at times leading to significant but very small effects with little pragmatic value and (2) it discourages the researcher from strategically modifying treatment (i.e., response guided experimentation) that may positively impact most if not all the patients. [FN94]

\*385 In contrast, under SSRD, patient responsiveness is probed through modification of, and changes in, the treatment as a consequence of response-guided experimentation. [FN95]

Ultimately, the objective driving drug development must be the improvement of patient health. The medical community effectively engages in a simulation of SSRD through often creative patient-by-patient treatment with biopharmaceuticals under its discretion to use them off-label--a "cart before the horse approach" so to speak. In the words of some thoughtful observers, "[t]o 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." [FN96]

SSRD's focus on the individual has made the methodology a natural fit for the field of behavior analysis. [FN97] In fact, much of the groundwork is attributable to B.F. Skinner and dates back to the 1930s:

Skinner emphasized studying the individual to determine lawful models of behavior. He drew heavily upon animal research, often using pigeons or rats, to uncover fundamental learning principles that could then be applied to humans. Inevitably, similar procedures for modifying behavior were applied to individual human subjects. Within the realm of applied behavior analysis, single subject design studies began examining methods for modifying behavior of individuals with diverse psychological problems, including stuttering, learning disabilities, mental retardation, and psychotic symptoms. [FN98]

SSRD has had a profound impact in the treatment of individuals with autism spectrum disorder and other severe learning disabilities. [FN99] For example, the CABAS® model, a comprehensive approach to behavior analysis and schooling, [FN100] has yielded an abundance of procedures, tactics, interventions, and large scale protocols for parents, educators, and children with a wide \*386 variety of disabling conditions. [FN101] The underlying theme of all CABAS® research is adhering to scientific rigor based on John Stuart Mill's five canons of the scientific method. [FN102] Through tightly controlled scientific studies conducted by practitioners, CABAS® research has promoted the growth and development of academic social repertoires for children, and generally enabled learning and function in thousands of children deemed "unteachable." [FN103] While education is a field susceptible to trends, untestable theories, and heavy reliance on construct attributes, SSRD has allowed the field of behavior analysis to establish grounded, effective approaches and documented success with severely learning-disabled children through natural science evaluation in human clinical research. Interestingly, while SSRD methods have been developed through and used significantly in ABA, they have been used infrequently in clinical psychopharmacology.

## II. Drug UnderDEVELOPMENT

Throughout much of the twentieth century and into the present one, pharmaceutical research and development (“R&D”) has been the most profitable sector. [FN105] For decades, our tendency as patients and consumers has been to believe that prescription medications improve human health and, in turn, to associate medicine closely with science--especially when grappling with a seriously debilitating illness. [FN106] There have been profound improvements to human health through pharmaceuticals for well over a half century, [FN107] but the overall reality is that the prescription medication arsenal to treat all human ailments prior to the 1990s consisted of merely 2000-3000 commercial pharmaceuticals derived from 483 drug targets (compounds that serve as the basis for medicinal applications). [FN108]

### \*387 A. The Twentieth Century Drug Development Experience

The crudeness of the underlying science relied upon is self-evident in the twentieth century drug development experience. Historically, developers would sort through thousands of drug targets to produce just one pharmaceutical success. [FN109] The endeavor focused on taking away the symptoms of disease--not on understanding and treating the causes of disease. [FN110] “[D]rug discovery essentially was a linear process based upon screening and testing of thousands of chemicals and natural substances for potential therapeutic activity. Screening was time consuming and largely random because drug targets and drug functions were in most cases unknown.” [FN111] Compounds were introduced in living organisms to identify their effect and potential medicinal utilities, purified to control toxicity in conjunction with at least one medicinal use, and introduced onto the market with the expectation that physicians would experiment further while practicing medicine on patients and identify additional clinical utilities through off-label uses. [FN112]

Drug sponsors were not even required to demonstrate efficacy for market access until 1962. [FN113] The regulatory standard for market approval of a drug candidate in the United States has been eliminating symptoms, even if just marginally more effectively than a placebo, coupled with a showing that adverse events and other safety issues across the target disease population are tolerable given the benefits. [FN114] This standard, paired with the discretion of \*388 commercial sponsors to tailor clinical research and to apply (or not) for approval of specific uses in applications for market access, has invited tremendous off-label use by the U.S. medical profession once products reach the market. [FN115] Though the biopharmaceutical sectors spend tens of billions of dollars on research annually, [FN116] they spend more on marketing--both legal and illegal. [FN117] Much of their marketing is directed at encouraging the medical community to exercise its discretion to use their products off-label. [FN118] Off-label use is motivated further by publication of industry-sponsored research in science and medical journals, direct-to-consumer marketing, [FN119] and patient faith in new treatments, including experimental ones. [FN120] Even when marketed legally, only “[o]ne-third of all drugs act as expected when prescribed to patients,” and there are approximately two million adverse drug reactions requiring

hospitalization each year. [FN121] Adverse drug reactions cause more than \*389 100,000 deaths annually in the U.S.--meaning that more people in the U.S. die from legal use of prescription medications than from automobile accidents. [FN122] Medicine remains much more art than science:

Even today, with a high-tech health-care system that costs the nation \$2 trillion a year, there is little or no evidence that many widely used treatments and procedures actually work better than various cheaper alternatives.

....

. . . And while there has been progress in recent years, most of these physicians say the portion of medicine that has been proven effective is still outrageously low--in the range of 20% to 25%. [FN123]

## B. Today's Drug Research and Development Potential

Drug development has changed fundamentally. [FN124] The legacies of discretion to commercial sponsors over the content of clinical research and to the medical community over off-label use are prevalent today, but the science of drug development has evolved and is undergoing a genomics (genetic expression) metamorphosis--a "genomics revolution." [FN125] The prevalence of "biopharmaceuticals" in the drug development pipeline and the centralized review of all new drugs, whether based primarily in biology or chemistry, within the Center for Drug Evaluation and Research (CDER) beginning in 2004 [FN126] confirm that pharmaceutical R&D and biotech have integrated extensively. [FN127]

\*390 The potential of ongoing drug development, with a map of the human genome in hand [FN128] and the creation of more profound tools underway, [FN129] arguably is limited only by human ingenuity given increasing abilities to manipulate the "highly sophisticated, delicate regulatory pathways and \*391 feedback loops" [FN130] of drug targets through the precision of genetics and identification of environmental influences. [FN131] Today holds the promise of infiltrating disease pathways on the cellular, genetic, and molecular levels to treat the causes of disease and thereby improve human health well beyond existing capabilities. [FN132]

The completion of the human genome map in 2003 made it possible to identify an individual's genetic makeup to determine disease risk, and a patient's likely response to certain medications. Genetic information may be used to diagnose a condition in an individual prenatally or prior to the presentation of any clinical symptoms. [FN133]

Millions of associations have been made between genetic variations and human health, and each constitutes a potential drug target. [FN134] Increasingly, discussion of a forthcoming era of personalized medicine--engineering medications tailored to individual patient's genetic makeup (pharmacogenetics, developed through pharmacogenomics) [FN135]--and extensive genetic profiling as part of both preventive care and treatment carries a tone of "when" rather than "if." [FN136] Overall, there is considerable consensus that "the availability of the \*392 human genome sequence, together with the

pharmacogenomic and pharmacogenetic approaches to developing new drug therapies, has and will continue to contribute to a better selection and faster development of safer and more effective diagnostics and treatments.” [FN137] Affirmations of the health care potential of contemporary biopharmaceutical R&D include Herceptin, [FN138] Gleevec, [FN139] and Olaparib. [FN140]

### C. Drug Disappointments and Desperation

Unfortunately, the present reality is that drug development lingers between the scientifically crude, yet enormously profitable pharmaceutical past and the biopharmaceutical present and future. [FN141] “Ten years after President Bill Clinton announced that the first draft of the human genome was complete, medicine has yet to see any large part of the promised benefits.” [FN142] The transition could take many years--decades according to some commentators. [FN143] In recent years, drug development disappointments have vastly outnumbered successes in spite of tremendous investment. [FN144] According to the pharmaceutical industry's trade organization, the Pharmaceutical Research and Manufacturers of America (“PhRMA”), “In 2009, America's pharmaceutical research and biotechnology companies continued to make the \*393 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.” [FN145] Nevertheless, new drug approvals fell to a twenty-five year low in 2007, just eighteen, followed by a slight bump to twenty-four in 2008 and twenty-six in 2009. [FN146] In 2010, Pfizer Inc., the world's largest research-based pharmaceutical company, did not produce a single new drug approval. [FN147] In comparison, new drug approvals peaked in 1996 when the FDA approved fifty-three. [FN148] According to Dr. Francis Collins, Director of the National Institutes of Health, this decline in productivity over the past fifteen years “certainly doesn't show any signs of turning upward.” [FN149] In fact, the federal government has become concerned enough about the performance of the commercial biopharmaceutical sectors to start a “billion-dollar government drug development center to help create new medicines.” [FN150] Industry continues to spend enormous amounts of money to make new drugs. [FN151]

The drop in new drug approvals has taken place in spite of annual governmental investments of billions of dollars in biomedical research and a substantial increase in commercial investment in biopharmaceutical R&D. “Before 1980, the National Institutes of Health (NIH) funded most medical research. . . . Today, drug and medical device companies fund up to 80% to 90% of all clinical trials; in 2005, industry invested 78% more in research and development than did the federal government.” [FN152] Though the trend is to export clinical research beyond the U.S. borders and to outsource it to CROs, [FN153] the amount of clinical research undertaken today within the United States is unprecedented-- an almost fifty percent increase during the first half of this decade. [FN154] Phase III trials have expanded to 20,000 subjects from just \*394 3,000 five years ago, which has doubled their cost--now typically \$50-100 million. [FN155]

In addition to the decline in new drug approvals, many of the prescription drugs the FDA has put on the market in recent years have proven disappointing. There is ample reason to question their quality and the Agency's performance overseeing them. [FN156] Most notably, Vioxx has become a “scarlet letter”

the FDA is likely to wear for years to come, [FN157] and many additional prescription drug problems have followed in recent years. In the fall of 2010, the FDA itself “concluded that in some cases two types of drugs that were supposed to be preventing serious medical problems were, in fact, causing them.” [FN158] These were Avandia, prescribed heavily to treat type-2 diabetes, and bisphosphonates--an active agent in the prescription drugs Fosamax, Actonel, and Boniva--used widely to prevent fractures common in people with osteoporosis. [FN159] Avandia was associated with an increased risk of heart attacks and strokes, a major problem for its target patient group given two thirds of diabetics die of heart problems, [FN160] and bisphosphonates was \*395 determined to actually cause fractures of the thigh bone and degeneration of the jawbone. [FN161] In addition, a whole generation of teenagers with severe acne was treated with Accutane, on the market in 1982, which now is associated with inflammatory bowel disease, ulcerative colitis, Crohn's disease, other gastrointestinal disorders, liver damage, birth defects, and suicidal thoughts. [FN162] Roche, the manufacturer, pulled Accutane from the market on June 29, 2009. [FN163] Many commercial drug developers and their supporters blame the FDA for the drop-off in new drug approvals, claiming the FDA has been too strict. [FN164] Others attribute the fall to an industry that is clinging to the low science and regulatory standards of the past, stretching the commercial lives of pharmaceuticals through manipulation of the patent system, and contriving “me too” drugs rather than engaging in genuine innovation. [FN165] When the Vioxx controversy substantiated doubts about the FDA's reliability in regulating the biopharmaceutical market, [FN166] the Agency responded by raising \*396 its level of scrutiny, which has generated substantial drug sponsor demand for specialized toxicology studies by CROs. [FN167] In fact, Vioxx and related concerns about FDA effectiveness inspired inquiry and generated corroborating reports on deficiencies from the Government Accountability Office (“GAO”), the Institutes of Medicine (“IOM”), and congressional hearings. [FN168] These \*397 questions about the sufficiency of drug regulation and overall agency performance prompted FDA Commissioner Margaret Hamburg, when newly appointed, to establish a task force with the mission of developing recommendations to increase transparency of the Agency's activities and decision-making. [FN169]

Avandia illustrates a trend that accompanied modernization of the Agency through the FDAMA: conditional market access with reliance upon post-marketing studies for safety and efficacy assurances. [FN170] With the introduction of user fees under the PDUFA [FN171] and modernization through FDAMA, [FN172] the Agency has approved drugs based upon surrogate endpoints-- indications that the drug performs, rather than definitive proof--and conditioned upon follow-on clinical studies. [FN173] Sixty-four drugs reached the market conditionally between 1992 and 2008. [FN174] According to the GAO, the FDA has allowed drugs to stay on the market even when follow-up studies showed they did not save lives. [FN175] Although more than one-third of these conditional studies are pending, the FDA never has pulled a drug from the market because of a failure to do required follow-up about actual benefits--even when the information is \*398 more than a decade overdue. [FN176] This failure is consistent with GAO and IOM declarations that the FDA's performance post drug approval is substandard. [FN177]

The very integrity of contemporary drug science has been called into question. Arguably, “government interventions are necessary to protect and preserve the public nature of science, which is essential to

shore up the contemporary science enterprise.” [FN178] Aggressive integration of academia and industry has created a proliferation of conflicts of interest, and the public nature of science--collegiality, communication, transparency, and accountability--has shifted in the direction of secrecy. [FN179] In the words of one observer, “It has turned universities into commercial entities, created a multibillion-dollar industry of technology transfer, and subsidized virtually every biotechnology company and discovery of the past twenty-five years.” [FN180] The science publications depended upon for scrutiny, accountability, and human health assessment have also embraced commercialization--evident by conflicts of interest controversies and the journals' imposition of high cost barriers to access their publications: [FN181]

\*399 The vast capacity to publish research and to share knowledge is tainted by conflicts of interest which threaten the reliability and integrity of the peer review process and, consequently, the underlying research. Governments, professional societies, and most science journals have failed to introduce and enforce the mechanisms necessary to manage conflicts of interest in an era of aggressive commercialization with meaningful confidence.

Also, industry has directly increased its influence over government and the general public substantially over the last few decades. [FN182] PDUFA legislation, [FN183] direct interface between industry and the broader government through extensive lobbying, [FN184] and direct communication with the general public through billions of dollars invested in marketing annually have raised concerns and inspired calls for more regulation. [FN185]

### III. Law-Policy Alchemy: A Proposal to Change the Science Standard in Human Clinical Research from Gold to Platinum

The FDA science standard for drug approval and the law-policy implementing it are, at best, dangerously dated--to the detriment of drug development, the practice of medicine, and human health. [FN186] Nevertheless, the commercial interests vested in new drug development, domestic and international, are too influential and too wedded to GD for an expansive break from the past to be a realistic possibility in the foreseeable future. [FN187] Under PDUFA, which generates the salaries of more than 900 FDA reviewers through the collection of user fees, industry has tremendous ongoing negotiation leverage given the inclusion of five-year sunset provisions in each PDUFA renewal coupled with two decades of FDA financial dependence for a considerable portion of its new drug review operating budget. [FN188]

Arguably, wholly uprooting the entrenched science standard, even if this were a viable option, would not be desirable given the approximately fifteen-\*400 year timeline to develop each innovative new drug and the transitional nature of ongoing science in the drug development pipeline. [FN189] Such a major change, especially if forced through law-policy that imposes more clinical trial obligations, could chill investment in pharmaceutical R&D, which is sorely needed during this time of historically high drug



development costs, product disappointments, and economic challenges that extend well beyond the biopharmaceutical sectors. [FN190]

Although drug development is evolving in the direction of precision through genomics (genetic expression), [FN191] proteomics (protein expression), [FN192] and related fields, overall, the endeavor still remains too crude to adopt SSRD as a substitute for traditional GD. [FN193] As observed by the FDA's Janet Woodcock, an agency leader under several presidential administrations, both Democratic and Republican, "At this time, medical practice is predicated on observation. For example, we still collectively categorize lung cancer as we did one hundred years ago. We still are not sophisticated. We don't know what the actual molecular cause of that particular cancer is in that particular person because we don't look for it." [FN194] However, the biopharmaceutical sectors certainly have the resources and capabilities to rise to the occasion of a higher standard in clinical research than traditional GD. [FN195]

\*401 A meaningful, pragmatic transition is needed: SSRD should be introduced as a complement or nested research methodology to GD to shift more meaningful understanding of pharmaceuticals from clinical care (the delivery of health care to patients) to clinical research; to lessen experimentation on patients in the delivery of their care through physician off-label use, which is removed from regulations to protect human subjects; [FN196] and to infuse responsiveness to the increasing precision enabled in both drug development and the delivery of care by contemporary genetic science. [FN197] "For biomedical \*402 researchers, the best course for increasing scientific understanding of relevant phenomena revolves around the utilization of a variety of methodological designs, with the research question of interest determining the choice of the design." [FN198] Although meaningful SSRD data could complicate GD trials and lengthen the drug approval process, understanding pharmaceuticals much more before they reach the market is sorely needed. [FN199] Moreover, it is a cost that could be contained through incremental implementation and potentially offset through a reduction in the lost opportunities attributable to drug underdevelopment. Although SSRD presumably would narrow the existing opportunity to oversell by making new drugs more thoroughly understood prior to their market entry, the extra data could raise the presently waning confidence of providers and patients--a "one-two punch" of science. From a regulatory perspective, infusing more specificity into the product approval process, knowing much more about pharmaceuticals prior to putting them on the market, and, consequently, restricting the familiar level of off-label use are desirable and needed--and demanded increasingly by government policy makers and the general public. [FN200]

The following discussion establishes the potential of SSRD to improve drug development and health care delivery, with emphasis on the practicality and feasibility of incorporating SSRD into human clinical research. After identifying law-policy options, the Article emphasizes the use of positive commercial incentives based upon enacted legislation that has succeeded in getting desired human clinical trial research undertaken by industry--namely the BPCA and the ODA, each of which is addressed in the following discussion.

#### A. SSRD's Potential to Improve Drug Development and Delivery

Wait-and-see dependence on the medical profession to sort out the impact of prescription medications on individuals, one patient at a time, in a trial-and-error manner, “exposes patients to potentially harmful drug interactions and \*403 delays potentially effective or the ‘right’ treatment.” [FN201] As recognized by Dr. Janosky, an expert in SSRD, there is a strong parallel between SSRD and the actual delivery of health care:

In a primary care setting, the patient generally exhibits symptoms and the physician follows evidence-based or appropriate steps to treat these symptoms. 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. [FN202]

SSRD, the very nature of which is close scrutiny of each of the individuals under study, [FN203] could improve decision-making during the clinical trial process and actually increase flexibility in clinical research for drug development because it presents an opportunity to tailor interventions for specific subjects and to modify ineffective ones over the course of the period of study. [FN204] A major practical advantage of SSRD over GD is that “[i]t overcomes some of the inherent limitations found in large-scale clinical trials, in that treatments are tailored for unique individuals and can also be modified over time.” [FN205] SSRD data could better enable sponsor decision-making for its GD counterpart, thereby saving them from investing hundreds of millions of dollars in the development and marketing of products like Vioxx, Avandia, and Accutane, each of which has exposed their manufacturers to substantial product liability and class action lawsuits. [FN206] By addressing human variability through SSRD, drug sponsors could cut back significantly on the time and expense of human clinical trials that are required to put new drugs on the market, both of which have risen significantly in recent years. [FN207] Moreover, there is an obvious ethics advantage in that many SSRD designs ensure that \*404 each individual receives the treatment(s) and does not require denying patients access to potential treatments to create a control--a standard component of GD. [FN208] SSRD could even enable research not practicable under GD. [FN209] As explained by Professor Janosky,

Specifically, at times it is difficult to find a large number of patients who have unique demographics or suffer from rare diseases. Furthermore, large N studies can be time consuming. One of the consequences of the time consuming nature of large N research is the difficulty in studying public health crises, for example. Additionally, the exorbitant financial costs of large-sample research often limit who is able to conduct such projects, at times risking an ethical dilemma with the linking of the researcher and the funder in mutual vested interests in the results. For example, funding from pharmaceutical companies is often needed to conduct the multi-million dollar research necessary for evaluating the same drugs those companies produce. [FN210]

SSRD, with its emphasis on responsiveness to human variability, offers an opportunity to identify genetic markers and to develop meaningful biomarker screens during the human clinical trial process. Specifically, SSRD introduces an opportunity to use the clinical trial process to develop a bouquet of

sophisticated genetic screens--for example, genetic tests that stratify patients in the trials to discern those most prone to responsiveness and those at higher risk for adverse events, and perfecting drug dosage on a person-by-person basis. [FN211] Genetic differences impact responses to pharmaceuticals, and at times do so profoundly. [FN212] Studies establish that enzyme variations in genes, with thirty or more enzymes typically coded for each gene, may have a profound impact on the rate that they are metabolized--a major consideration for what constitutes safe and effective dosing for individual patients. [FN213] A noted illustration is the wide variation in patient reactions to asthma medications, \*405 some of which studies have attributed to identified differences in genetic makeup. [FN214]

## B. The Feasibility of SSRD in Drug Development--Precedent and Practice

Several trends suggest that drug sponsors should expect more scrutiny and demands for accountability from regulators, the medical community, and the general public: rising health care finance pressures, federal and state, domestic and international; increased transparency of market performance and market behavior through internet communication, including organized observation through patient and consumer protection groups; and pressure on the FDA to increase post-marketing regulation requirements and general enforcement. [FN215] SSRD could prove a means to meet and quell these pressures, and implementation is practicable: there is precedent for the use of SSRD in human clinical research to advance health care, albeit almost entirely outside of the context of biopharmaceutical development. [FN216]

Extensive SSRD human clinical research has been done in applied behavior analysis and education, [FN217] and “[n]umerous studies have highlighted the importance of the single subject design paradigm in primary care.” [FN218] Some especially notable disease-related group accomplishments utilizing SSRD include a large portion of the research studying treatments for aphasic patients (loss of the ability to articulate ideas or comprehend language due to brain damage from injury or disease), attention deficit hyperactivity disorder (“ADHD”), and diabetes. [FN219] Many SSRD studies in the primary care setting have been premised upon raising the predictability of responsiveness to stimulant medications at various dosages, including an ambitious collective assessment study carried out in Australia more than two decades ago. As summarized by Professor Janosky,

[I]n the 1980s, McMaster University designed a service for community and academic physicians to facilitate the planning and conduction of single subject (N-of-1) trials. The effectiveness of the trials was evaluated by the physicians' management plans and confidence levels in the plans both prior to and following trials. A total of 57 single subject trials were completed, with 50 trials providing a definite clinical answer and 15 resulting in the physician \*406 altering patient treatment. In those 15 trials resulting in treatment adjustment, 11 trials lead to physicians discontinuing the medication therapy they planned to administer indefinitely. Trials that were not completed generally stemmed from patient' or physician' noncompliance or patient' concurrent illness [sic].

Based upon these results reported by the collaborative team at McMaster University, single subject trials afford important opportunities for application in biomedicine, including directly improving patient clinical care. [FN221]

SSRD experience in human clinical trials and in the primary care context over decades could be infused into drug development readily, creatively, and with flexibility, as demonstrated by Professor Gina Green:

Unlike between-groups studies, single-case studies can be conducted in typical service settings like schools, treatment centers, hospitals clinics, and homes. Their focus on the development of individual behavior and their flexibility makes these methods especially well-suited for studying treatments for [autism spectrum disorders], given the large individual differences among people with those diagnoses. Single-case research methods also afford a means for practitioners as well as researchers to evaluate the effects of many types of treatments--behavioral, educational, medical, or combinations--with scientific rigor. [FN222]

A report issued by the IOM in 2001, which provided initial guidelines for small clinical trials, is an affirmation of the feasibility and potential utility of SSRD in drug development. [FN223] The report recognized the potential utility of these trials for a portfolio of situations, including rare diseases, unique study populations, individually tailored therapies, isolated environments (for example, health care in rural areas), emergency situations, and public health urgency. [FN224]

An SSRD component to clinical trials for drug development would introduce several potential benefits, in addition to raising fundamental understanding about new drugs during the pre-market clinical research stage. The size and costs of GD trials have increased immensely in concert with the proliferation of the genetic sciences and associated precision--which by its very nature demands increased attention to human variability. [FN225] The GD approach is demonstrating decision-making confusion and clinical trial \*407 failures. [FN226] As observed in an April 2010 report issued by the Institute of Medicine, approximately forty percent of all advanced clinical trials sponsored by the National Cancer Institute, organized under the GD gold standard for the most part, are never completed--resulting in a waste of money, effort, and lost opportunities to improve human health and reap financial returns. [FN227]

An obvious primary question for implementation of SSRD is, given industry's entrenched commitment to GD, how to use SSRD and GD together in drug development. Johnston and Pennypacker, authors of a heavily-cited text on behavioral research that compares and contrasts SSRD and GD, propose that, where both are used, SSRD should be utilized to graph and check data for each subject as a quality control on GD reliance on inferential statistical techniques and interpretation to generate and explain data. [FN228] In fact, they believe that all data should be subjected to SSRD scrutiny before it even is eligible for use in GD. [FN229] Their primary concern is that group data risks obscuring individual patterns of responding:

[T]he more an analytical procedure changes the investigator's picture of the subject's behavior as it actually happened, the greater the risk that the analytical procedure may exert more control over interpretations than do the data. . . .

A related guideline may be stated as follows: The more an investigator has to change the data to see something important, the greater the risk that the result is not that important or, perhaps, not even there. [FN230]

To begin the transition into utilization of SSRD in biopharmaceutical R&D, [FN231] one option is to pursue running SSRD and GD trials in parallel and throughout Phases I-III of the pre-market human clinical trial process. [FN232] Incorporating the Johnston and Pennypacker approach, SSRD trials could be started in advance and used to shape GD trials, and then as a quality control \*408 throughout their duration. [FN233] Another possible approach would be to use SSRD more intensely in a focused capacity--perhaps for specific trials, specific patient subpopulations, or for specific treatments, such as those for rare patient populations in conjunction with the Orphan Drug Act. [FN234] Specifically, "single subject designs may be nested within larger clinical trials to increase compliance and answer more detailed questions. Single subject designs are particularly useful for answering questions regarding rare diseases, side effects, unique populations, emergency situations, and isolated environments, in which between-group designs would be unfeasible or impractical." [FN235]

Another option, and one that could be applied in conjunction with the others, would be to introduce SSRD services to assist physicians with market use of prescription drugs as an extension of Phase IV trials--an application strongly supported by the McMaster University study and ample primary care applications. [FN236] In summary,

Research supports the effectiveness of the single subject design, from studying treatments for rare patient populations to providing N-of-1 trial services in assisting physicians. The single subject design is an innovative addition to the arsenal of available methodologies for primary care physicians, biomedical students, residents, medical research faculty, clinical practitioners, among others. Consistent with the NIH Roadmap Initiative, increasing awareness of the utility in the single subject design could enhance treatment approach and evaluation both in biomedical research and primary care settings. [FN237]

#### \*409 C. Law-Policy Catalysts to Turn Gold into Platinum

Although "there is substantial proof that the current method of creating medicines for the general public is problematic and could prevent effective treatments from reaching the marketplace" , [FN238] voluntary uptake of SSRD by drug developers is unlikely. They are inclined to resist the official addition of SSRD into the regulatory process for the same reason they have been slow to introduce pharmacogenomics data (R&D based upon genetic expression [FN239]) in their applications in spite of FDA encouragement--fear that it will be used against them to limit their market reach. The FDA has issued voluntary guidelines to promote submission of pharmacogenomics data which, in sync with SSRD, innately involves closer individual patient scrutiny--including at the genetic and molecular levels--and more extensive patient-centered data compilation during the clinical trial process. [FN240] Unfortunately, the guidelines \*410 have not overcome industry fear that genetic specification will break down disease groups and restrict market reach through narrower approvals, more defined product

labels, reimbursement limitations, and less physician discretion to use these pharmaceuticals off label. As explained by Dr. Woodcock,

The primary policy problem right now is that most of these genetic tests are not being evaluated in clinical studies, and they are not being seen by the regulatory agencies. Application in the official drug development regulatory process is stymied by concern about how these tests will be used by the marketing application reviewers. This could present a real lost opportunity for any person who wants to take medicine in the foreseeable future. [FN241]

Even when pharmacogenomics data make it onto drug labels, [FN242] the underlying sponsor data released is limited, and the medical community often lacks the knowledge to make efficient use of it. [FN243]

A thoughtful law-policy intervention beyond voluntary guidelines is essential to add a meaningful SSRD component to drug development. 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 commercial freedom that is the touchstone of our private market system and introduce susceptibility to legal \*411 challenges. [FN244] The drug development regulatory regime embodies deference to commercial free speech, proprietary interests, profit incentives, and the discretion to practice medicine--as the FDA has been reminded by Congress and through several legal challenges during the genomics revolution. 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." [FN245] As for legal challenges, in 2000 the U.S. Court of Appeals for the District of Columbia dismissed a challenge to FDAMA provisions addressing manufacturer promotion of off-label use that claimed the provisions imposed an undue burden on commercial free speech in violation of the First Amendment. [FN246] However, the Court based its decision on the fact that the parties reached agreement that there was no longer an issue after the FDA changed its stance. [FN247]

Perhaps the most vivid recent illustration of the limits of agency authority to force studies on drug sponsors is the FDA's attempt to fill the vacuum of pediatric studies for pharmaceuticals known to be prescribed to children. [FN248] In \*412 fact, even today, pediatric data is insufficient, at times wholly lacking, for two-thirds of prescription drugs. [FN249] A 1994 study reported that six of the ten drugs most commonly prescribed to children had inadequate pediatric labeling, [FN250] which inspired the FDA to issue a rule and to introduce a voluntary, incentive-based program to promote pediatric testing and labeling. [FN251] The tone during this time, under David Kessler who was the FDA Commissioner from 1990 to 1997, was administrative caution:

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.

To address this dearth of pediatric data even for drugs prescribed to children routinely, Congress codified a voluntary, incentive-based five-year program through a pediatric exclusivity provision in FDAMA. [FN253] This program granted drug manufacturers six months of market exclusivity for their products--as opposed to just extending intellectual property rights--as an incentive for conducting pediatric studies. [FN254] The FDA then went further and issued a "Pediatric Rule" in 1998 that mandated pediatric testing-- both for drug candidates and those already approved for market use. [FN255] The FDA was \*413 sued successfully under the Administrative Procedure Act [FN256] with claims that promulgation of the Pediatric Rule was arbitrary and capricious and exceeded the FDA's authority. [FN257] The voluntary program worked but was only moderately successful. As of April 2001, the FDA had issued a mere 188 written requests covering 155 drugs already on the market and just thirty-three new drugs not yet approved. [FN258] "As of April 1, 2001, only 28 drugs had been granted periods of exclusivity." [FN259] Most of these drugs did experience a labeling change of some degree to address pediatrics, but, according to an article published in 2001, only 37.5 percent constituted a significant change in safety or dosing. [FN260] By discussions in 2001 to reauthorize the voluntary program, only twenty-five percent of drugs had been studied in children--just a five percent increase from the 1994 statistic. [FN261]

While the litigation against the FDA rule was pending and the FDAMA voluntary program approached its January 1, 2002, sunset, [FN262] Congress intervened with the Best Pharmaceuticals for Children Act. [FN263] BPCA reinstated the FDAMA voluntary program for pediatric testing with the incentive of six months of market exclusivity and then went further by empowering the FDA to step over manufacturer resistance and get pediatric trials done by third parties through the National Institutes of Health or with funding from a federal trust. [FN264] BPCA also provided a basis to strike the FDA's Pediatric Rule. [FN265] Regarding the BPCA's effectiveness, critics have \*414 pointed out that the BPCA approach shifted considerable drug development cost from manufacturers to taxpayers. [FN266] Nevertheless, as of March 2004, pharmaceutical manufacturers had issued 346 requests to evaluate prescription drugs for pediatric use, ninety-seven drugs were granted six months of exclusivity, and new labels were approved for seventy. [FN267] As of 2008, 145 drugs had been issued exclusivity. [FN268]

Another illustration of the success of Congress and the FDA to utilize positive commercial incentives to get desired clinical research undertaken in drug development is the Orphan Drug Act. ODA is a rewards-based program that makes it commercially viable to develop drugs for small groups of patients through tax incentives, a seven-year period of market exclusivity, and other benefits. [FN269] The targeted research is being done: some 350 orphan drugs have been approved in the U.S. market alone, and the program has been replicated by other countries. [FN270] Orphan drug filings have increased, especially submissions from multinational pharmaceutical sponsors. There is considerable overlap between the ODA methodology and suggestions from NIH and others to incorporate small clinical trials and SSRD into drug development with an initial focus on small, discernible patient groups.

The effectiveness of commercial incentives to get desired clinical research done has been demonstrated through ODA and BPCA, as has the \*415 ineffectiveness of soft incentives such as voluntary guidelines and the susceptibility of FDA mandates to legal challenge. To implement SSRD into drug development as quickly, effectively, and pragmatically as possible, Congress and the FDA should build upon what has

worked and an opportunity introduced by a new government initiative--introduction of a federal research center with the specific mission of helping industry overcome drug development difficulties. Given the commonality between ODA--small, distinguishable disease groups--and SSRD, ODA should be modified to favor utilization of SSRD in program qualification and provide additional incentives for its use, including additional tax incentives, additional reviewer support and responsiveness, and an additional extension (at least one year, to make the total exclusivity eight years) of market exclusivity for approved products that complete SSRD studies. The FDA would have the discretion, as it does with the base ODA program, to set criteria and determine eligibility--meaning the Agency could experiment with SSRD to assess its efficacy in varied applications.

For drug development beyond the small disease groups that qualify for ODA status, Congress and the FDA should draw heavily from BPCA--perhaps in a manner that, in addition to promoting SSRD overall, particularly favors use of SSRD in pediatric studies and studies of other distinguishable patient and disease groups to make up for the relative dearth of data over the years. This approach would be closely consistent with the suggestions of SSRD experts in disciplines that have embraced the approach, including professors Green, Janosky, Johnston, and Pennypacker. [FN271] SSRD studies should be solicited with the incentive of at least six months of additional market exclusivity for resulting products (pediatric studies with SSRD would be rewarded with a year or more of product exclusivity), and Congress should create a separate trust fund to enable the FDA to undertake these studies when industry sponsors refuse. The fund should be established to direct the FDA to include post-marketing (Phase IV) studies with primary care physicians on both new and existing drugs to assist physicians with market use--along the lines of the McMaster University study and suggestions of Dr. Janosky. [FN272] Both the IOM and GAO have determined that the FDA does a grossly insufficient job once pharmaceuticals reach the market and recent experience with the disappointment of approved drugs confirms, suggesting that SSRD studies, consistent with the practice of medicine, could make a substantial contribution. [FN273] An SSRD fund would impose a cost on taxpayers--a major \*416 criticism of BPCA. [FN274] Nevertheless, the state of drug development, new drug disappointments, the potential of SSRD coupled with genetic precision to improve drug development and benefit health care, the need to lessen dependence on years of physician off-label use for meaningful understanding of new drugs, consumption of government regulatory resources for this disappointing return, and lost product opportunities for sectors that are a major presence in our economy suggest that taxpayer investment in such a fund would be more than justified--especially given the amount of funding taken from industry in user fees to cover FDA operations. The federal government appears to have recognized as much through establishment of a billion dollar center to help industry create new drugs, headed by Dr. Francis Collins who led the U.S. government HGP effort and now is Director of NIH. [FN275]

This center to assist drug development also should make SSRD a priority. Although the Center is focused primarily on basic research--for example, to use its state-of-the-art robotic screening capabilities to identify chemicals that influence enzymes--and animal studies, its mission also includes starting human trials. [FN276] The center should broaden its clinical research vision and include SSRD. The transition into clinical research in drug development involves a substantial increase of industry investment--money, research, and opportunity. Contingent upon the outcome of research, investment correlates



with industry commitment--meaning an inclination to want to work with the center to resurrect troubled drug development efforts that hold market potential. The center, preferably working in conjunction with the FDA, could infuse SSRD to salvage developed drug R&D undertakings representing substantial time and research investments and financial investments of tens, if not hundreds, of millions of dollars. The Center's involvement in just Phase I trials could make significant contributions. [FN277]

## Conclusion

The so-called gold standard for human clinical research in drug development, GD, no longer glitters--to the extent it ever really did. The costs of relying too heavily on GD are self-evident, including a significant decline in new drug approvals in spite of historic investment and resources such as the map of the human genome, drug disappointments such as Vioxx and Avandia that have threatened the lives of the patients taking them and generated large \*417 class action law suits, and dwindling faith in the FDA as evident in the passage of the FDAAA in 2007 as well as the GAO and IOM reports issued in 2006. [FN278]

The crude science past in drug development, which may have justified reliance on GD, no longer should control the genetics present and future of human clinical research in biopharmaceutical R&D and FDA market approval. Genetics is increasingly dominating the drug development pipeline, and the very nature of genomics is unprecedented scientific precision--working at the cellular, genetic, and molecular levels in living organisms to identify genetic expression, to reveal the origins and progression of disease, and to make connections between the two and develop drugs based upon those connections. [FN279] Regulatory reform is needed to make the science standard for human clinical trials responsive to the significance of human individuality and variability--factors recognized innately in both genomics and the patient-centered practice of medicine.

This Article has proposed law-policy reforms to infuse an alternative science methodology into human clinical research for drug development--SSRD. SSRD shares the responsiveness of genetics-based R&D to the reality of individual human variability, and an SSRD complement to GD could prove a means to move drug development through its present state of puberty between the crude science past and genetics-based future. [FN280] "The single subject design has been successful in illuminating research findings across a variety of disciplines. It overcomes some of the inherent limitations found in large-scale clinical trials, in that treatments are tailored for unique individuals and can also be modified over time." [FN281]

The proposals to promote SSRD put forth in this Article are based upon commercial incentives and programs that have endured the threat of legal challenges--the ODA and the BPCA. [FN282] The FDA has successfully used ODA and BPCA to get needed clinical research done on small disease groups and children that industry had avoided. This Article also proposes to infuse SSRD into human clinical research through a billion-dollar government center recently established to help industry create new drugs. [FN283] The objective, as expressed by NIH Director Francis Collins who will direct the center and

headed the U.S. government's effort to map the human genome, is to convert contemporary genetic science accomplishments into clinical applications that \*418 improve human health and move industry out of its fifteen year slump in new drug approvals. [FN284]

The biopharmaceutical sectors have the resources and capabilities to meet a higher science standard in clinical research than GD--a standard that has resulted in ongoing drug underdevelopment. [FN285] SSRD is an opportunity to introduce a gold standard that actually glitters in an age of genomics and shifts drug development in the direction of needed improvements to human health.

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[FN1]. G. Steven Burrill, Polishing the Crystal Ball: G. Steven Burrill Predicts What's Ahead for Biotech in 2009, Burrill Report (Jan. 2, 2009), <http://www.burrillreport.com/article-980.html>. The FDA approved eighteen innovative new drugs in 2007, twenty-four in 2008, and twenty-six in 2009. Ed Silverman, How Many New Drugs Did FDA Approve Last Year?, Pharmalot (Feb. 18, 2011, 9:35 AM), <http://www.pharmalot.com/2011/02/how-many-new-drugs-did-fda-approve-last-year>; New Drug Approvals on Pace to Exceed 2008 Total, Res. Recap (June 9, 2009), <http://www.alacrastore.com/blog/index.php/2009/06/09/new-drug-approvals-on-pace-to-exceed-2008-total>. But see Miho Nagano, Big Pharma Looks for a Fix, Investor's Bus. Daily, Sept. 29, 2008, at A9

(stating seventeen approvals in 2007). See *infra* notes 146-49 and accompanying text.

[FN2]. Gardiner Harris, *A New Federal Research Center Will Help to Develop Medicines*, N.Y. Times, Jan. 23, 2011, at A1 (quoting Dr. Francis S. Collins, Director of the National Institutes of Health, in a story on the federal government's decision to launch a billion-dollar drug development center to help industry create new pharmaceuticals).

[FN3]. Alan Poling et al., *Pharmaceutical Interventions and Developmental Disabilities*, in *Developmental Disabilities: Etiology, Assessment, Intervention, and Integration* 105, 120 (W. Larry Williams ed., 2004). Poling's article also states that:

Few, 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.... The use of single-case research methods may make it easier to conduct research, although these methods have been used infrequently in clinical psychopharmacology.

*Id.* at 119.

[FN4]. This case study is derived from Dr. Gautreaux's work with children diagnosed with severe learning disabilities. "Emma" is a fictional name, and identifiers have been excluded to protect the family's privacy. Similar anecdotal and scientific accounts have been published. See, e.g., Catherine Maurice, *Let Me Hear Your Voice* 11-25 (1993).

[FN5]. See Am. Psychiatric Ass'n, *Diagnostic and Statistical Manual of Mental Disorders* 66-67 (4th ed. 1994) (describing the diagnostic features of "Autistic Disorder").

[FN6]. SSRD is explained *infra* at Part I.B. For illustrations of SSRD see, Janine E. Janosky et al., *Single Subject Designs in Biomedicine* 81-95 (2009). "The single subject design is a family of designs that share fundamental concepts and methodologies." *Id.* at 9. It is important to note that the literature often commingles single subject studies with "N-of-1" ("number-of-one") trials, which may be trials literally involving a single subject. Most SSRD experiments involve focused studies of and between multiple participants. Gina Green, *Single-Case Research Methods for Evaluating Treatments for Autism Spectrum Disorders*, 8 *Speaker's J.* 69, 73-74 (2008) (describing the SSRD method). For additional background information on SSRD and scientific research methods generally, see David H. Barlow et al., *Single Case Experimental Designs: Strategies For Studying Behavior Change* (3d ed. 2009) (discussing the origins of SSRD and detailing SSRD methods and issues); Murray Sidman, *Tactics Of Scientific Research: Evaluating Experimental Data In Psychology* 2 (1960) (discussing important points in evaluating scientific research); B.F. Skinner, *The Behavior of Organisms: An Experimental Analysis* (1938) (providing the foundation for modern-day behavior analysis); John Carey, *Medical Guesswork: From Heart Surgery to Prostate Care, The Health Industry Knows Little About Which Common Treatments Really Work*, *Bus.Wk.*, May 29, 2006, at 72 (discussing the benefits believed to be provided when using "evidence-based" medicine).

[FN7]. See Robert H. Horner et al., *The Use of Single-Subject Research to Identify Evidence-Based Practice in Special Education*, 71 *Exceptional Child* 165, 165-66 (2005); see also John O. Cooper et al., *Applied Behavioral Analysis 201* (2d ed. 2007) (describing multiple baseline design as a research tactic for evaluating treatment effects in behavior analysis); J. M. Johnston & H. S. Pennypacker, *Strategies and Tactics of Behavioral Research* 296-309 (2d ed. 1993) [hereinafter Johnston & Pennypacker, *Strategies and Tactics*] (discussing SSRD and GD in the context of behavior analysis); J. M. Johnston & H. S. Pennypacker, *Readings for Strategies and Tactics of Behavioral Research* 3-7 (2d ed. 1993) [hereinafter Johnston & Pennypacker, *Readings*] (discussing behavior analysis as a natural science); Alan E. Kazdin, *History of Behavior Modification: Experimental Foundations of Contemporary Research* (1978) (tracing the history of experimentation in behavior modification, a field that leans heavily on SSRD type methodologies); Steven C. Hayes, *Single Case Experimental Design and Empirical Clinical Practice*, 49 *J. Consulting & Clinical Psychol.* 193 (1981) (arguing that SSRD is a good fit for clinical psychology); Mark Wolery & Susan R. Harris, *Interpreting Results of Single-Subject Research Designs*, 62 *Physical Therapy* 445 (1982) (discussing the interpretation of SSRD results in the context of physical and occupational therapy); *infra* Part I.B. For thoughtful guidance on the use of SSRD in applied psychology, see Neville M. Blampied, *Single-Case Research and the Scientist-Practitioner Ideal*, in *APA Handbook of Behavior Analysis* (Gregory J. Madden ed., forthcoming 2012) [hereinafter Blampied, *Single-Case*]. For a tutorial on SSRD, see Neville M. Blampied, *Univ. of Canterbury, Single-case Research: Useful Tools for 21st Century Applied Science*, Address at the Society for the Quantitative Analyses of Behavior 34th Annual Meeting (May 28, 2011) (PowerPoint presentation on file with the Saint Louis University Law Journal) [hereinafter Blampied Presentation]. A video of Professor Blampied's tutorial presentation is available at <http://www.sqab.org/tutorials.php>.

[FN8]. Janosky et al., *supra* note 6, at 81-82; see *infra* note 42-43, 86-88 and accompanying text.

[FN9]. Janosky et al., *supra* note 6, at 81; see *infra* note 43 and accompanying text.

[FN10]. See *infra* Part I.B (offering a comparative discussion of GD and SSRD). Although averages may be compiled based upon the mode (a variable that occurs the most frequently), the mean (the total occurrence divided by the number of subjects), or the median (the occurrence in the lies in the middle) of a group under study, group design generally centers on determining statistically significant variations between the group that is receiving the treatment and those that are not. See Alan Poling et al., *Fundamentals of Behavior Analytic Research* 161-62 (1995); William W. Rozeboom, *Good Science is Abductive, not Hypothetico-Deductive*, in *What If There Were No Significance Tests?* 335, 335-38 (Lisa L. Harlow et al. eds., 1997) (discussing the pitfalls of significance testing); Stephen T. Ziliak & Deirdre N. McCloskey, *The Cult of Statistical Significance* 123-130 (2008) (detailing and criticizing the rise of statistical significance in psychology research); Statistical formulas are derived to account for complexity, but they are based upon these averages. Rozeboom, *supra*. Interestingly, “[a]veraging across individuals had its origins in a philosophical/religious attempt to remove the effects of original sin from measurement of humans.” Blampied Presentation, *supra* note 7, at 27.

[FN11]. Green, *supra* note 6, at 74; Janosky et al., *supra* note 6, at 81; David L. Morgan & Robin K. Morgan, *Single-Case Research Methods for the Behavioral and Health Sciences* 27-30 (2009); Jaan Valsiner, *Where is the Individual Subject in Scientific Psychology?*, in *The Individual Subject and Scientific Psychology* 11 (Jaan Valsiner ed., 1986). SSRD is discussed in detail *infra* at Part I.B. For an excellent, accessible summary of SSRD methodology, see generally *Blampied Presentation*, *supra* note 7. For discussion of SSRD in the context of applied psychology, see *Blampied, Single-Case*, *supra* note 7.

[FN12]. Janosky et al., *supra* note 6, at 81; see also Green, *supra* note 6, at 69.

[FN13]. See *infra* Part II.B. This Article focuses on human clinical trials, not basic (“bench”) studies. Reflective of the vast complexity and dynamism of human genetics--an estimated 23,000 genes responsible for all human variability, and the intense, ongoing interface of genes and environmental factors in human health--and the nascent state of genetic science at this time, there is tremendous dependence on group studies at the very beginning of the drug development continuum. American Health Lawyers Association's Advisory Council on Racial and Ethnic Diversity, *Patient-Tailored Medicine Part One: The Impact of Race and Genetics on Medicine*, *J. Health & Life Sci. L.*, Oct. 2008, at 1, 7 [hereinafter *Patient-Tailored Medicine Part One*]; American Health Lawyers Association's Advisory Council on Racial and Ethnic Diversity, *Patient-Tailored Medicine, Part Two: Personalized Medicine and the Legal Landscape*, *J. Health & Life Sci. L.*, Jan. 2009 at 1, 5-7 [hereinafter *Patient-Tailored Medicine Part Two*]. A rough map of the human genome determined “active” was completed just years ago (2003), and efforts to purify that map and to fully decode the human genome are still underway. Human Genome Project Information, U.S. Dept. of Energy, [http://www.ornl.gov/sci/techresources/Human\\_Genome/home.shtml](http://www.ornl.gov/sci/techresources/Human_Genome/home.shtml) (last updated July 25, 2011). Now scientists in the field of epigenetics are studying the “other human genome”--heritable changes in gene function that occur without a change in DNA. See Gary Felsenfeld, *A Brief History of Epigenetics*, in *Epigenetics* 16 (C. David Allis et al. eds., 2007); Adrian Bird, *Perceptions of Epigenetics*, 447 *Nature* 396, 396 (2007); see generally James A. Goodrich & Jennifer F. Kugel, *Binding and Kinetics for Molecular Biologists* (2007) (discussing qualitative measurements of biological binding reactions, “which are the fundamental building blocks of all complex biological systems”). For a richer discussion of the genome, see Eric H. Davison, *The Regulatory Genome: Gene Regulatory Networks in Development and Evolution* (2006). For further discussion of epigenetics, see the articles contained in *Epigenetics*, 293 *Sci.* 1063-106 (2001), and *NOVA: Epigenetics* (PBS television broadcast July 24, 2007), available at <http://www.pbs.org/wgbh/nova/sciencenow/3411/02.html>. In sum, at the base level of genetic science, comparisons are made between multiple individuals at the genetic level, at times entire populations (“biobanks”), to sort through this vast universe of variables and identify points for study. See generally *Symposium, Regulation of Biobanks*, 33 *J.L. Med. & Ethics* 1 (2005) (offering articles discussing biobanks and biobanking issues); *Symposium, Proceedings of “The Genomics Revolution? Science, Law and Policy”*, 66 *La. L. Rev. (Special Issue)* 1 (2005) [hereinafter *Genomics Revolution*] (offering articles discussing the necessity for biobanking to meet the needs of genomics research); see also Michael J. Malinowski, *Law, Policy, and Market Implications of Genetic Profiling in Drug Development*, 2 *Hous. J. Health L. & Pol.* 31 (2002) (noting the law, policy, and market implications of pharmacogenomics). Lars Noah, *The Coming Pharmacogenomics Revolution: Tailoring Drugs to Fit Patients' Genetic Profiles*, 43 *Jurimetrics J.* 1, 7-11 (2002) (discussing the potential for

pharmacogenomic research to enhance pharmaceutical therapies). Therefore, this Article appreciates the distinction between genetic studies at the molecular level from human clinical trials to treat individuals, and the discussion centers on the latter. Comparing the utility of GD and SSRD at the base level of drug development is beyond the scope of this Article.

[FN14]. “The first of the so-called miracle drugs, Sulfanilamide, led to the adoption of the Federal Food, Drug, and Cosmetic Act of 1938 which emphasized premarketing safety of drugs, based on scientifically designated animal and clinical studies.” Steven E. Pegalis, *American Law of Medical Malpractice* § 17:13 (3d ed. 2005).

[FN15]. It is important to note that, while “human variability” is assumed and considered innate to humans in group experimental design, in SSRD human variability is considered external and is able to be controlled by accounting for extraneous variables. See *infra* Part I.B.

[FN16]. See *Patient-Tailored Medicine Part One*, *supra* note 13, at 7: see generally *Genomics Revolution*, *supra* note 13 (offering articles discussing contemporary genetic science and issues in genomics). Genetic specificity in contemporary biopharmaceutical R&D is addressed *infra* at Part II.B.

[FN17]. As observed by other commentators in the context of patient-tailored medicine and race-based genetics research:

To predict therapeutic outcomes in individual patients, drug makers rely on statistical analyses of a targeted population's response to the medication in question. Thus, a practitioner's choice of drug often is based on population averages. Therefore, the current method of developing drug therapy focuses on large patient populations as groups, irrespective of the potential for individual, genetically-based differences in drug response.

*Patient-Tailored Medicine Part One*, *supra* note 13, at 7. The extent to which drug sponsors have been permitted to generalize over human variation in clinical research is extraordinary. For example, throughout most of the twentieth century, women and children typically were excluded from the groups studied to bring many of our familiar pharmaceuticals to market—including pharmaceuticals for conditions that impact women and children, such as asthma and heart disease. See Sarah K. Keitt, *Sex & Gender: The Politics, Policy, and Practice of Medical Research*, 3 *Yale J. Health Pol'y L. & Ethics* 253, 253 (2003). The rationale was to work to avoid groups deemed “protected” under federal regulations to protect human subjects—including women, the unborn, and children—and subject to more scrutiny, coupled with failure to appreciate the hormonal and other biological differences between men and women, adults and children, or the strategic choice to avoid complicating trials with factors such as the female hormonal cycle, menopause, and puberty. *Id.* at 254-55; Karen H. Rothenberg, *Gender Matters: Implications for Clinical Research and Women's Health Care*, 32 *Hous. L. Rev.* 1201, 1206-10 (1996). Accordingly, out of necessity, doctors prescribed medicines on the market to treat women and children in spite of a dearth of data about those uses. For example, the doses for children have been adjusted at doctor discretion based upon weight—similar to veterinary practice today. See Barbara A. Noah, *Just a*

Spoonful of Sugar: Drug Safety for Pediatric Populations, 37 J.L. Med. & Ethics 280, 281-82 (2009). The 1993 NIH Revitalization Act requires inclusion of women in Phase III clinical studies and gender-based analysis of research results. National Institutes of Health Revitalization Act of 1993, Pub. L. No. 103-43, §131, 107 Stat. 122, 133-35 (codified at 42 U.S.C. § 289a-2 (2006)). The Best Pharmaceuticals for Children Act (“BPCA”) codified patent extension incentives for drug sponsors to include children and created a trust fund for the FDA to do the same when drug sponsors refuse--conducting its own trials directly or through contracted third parties. See Best Pharmaceuticals for Children Act, Pub. L. No. 107-109, 115 Stat. 1408 (2002) (codified as amended in scattered sections of 21 U.S.C. and 42 U.S.C.).

[FN18]. In addition to the limitations of GD addressed throughout this Article, the efficacy standard for market approval based upon that data is to be better than a placebo or sugar pill, meaning to be better than nothing. See *infra* note 58 and accompanying text.

[FN19]. See *infra* Part III.A. Congress has responded to the problem, but this Article questions its fix through the Food and Drug Administration Amendments Act of 2007 (“FDAAA”) because of the ongoing fundamental reliance on GD. See *infra* notes 23-25 and accompanying text. “[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.” *Wash. Legal Found. v. Henney*, 202 F.3d 331, 333 (D.C. Cir. 2000). Off-label use of pharmaceuticals is generally accepted in the medical community and commonly practiced. *Wash. Legal Found. v. Friedman*, 13 F. Supp. 2d 51, 56 (D.D.C. 1998), vacated in part on other grounds *sub nom. Wash. Legal Found. v. Henney*, 202 F.3d 331 (D.C. Cir. 2000) (observing that “off-label use of FDA-approved drugs by physicians is an established aspect of the modern practice of medicine”); see *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 350 (2001) (noting that off-label use of medication is not only accepted in the medical community, but a “necessary corollary of the FDA's mission to regulate ... without directly interfering with the practice of medicine”).

[FN20]. The same often is true with new medical devices and procedures. An illustrative example of this point is the debate over when women should have mammograms. After decades of relying upon group numbers to strongly encourage all women over the age of forty years to have mammograms annually, the U.S. Preventive Services Task Force, based upon actual patient experience with the technology, now discourages the presumption and emphasizes the importance of a case-by-case, physician-patient, individualized approach. Danielle Dellorto, Task Force Opposes Routine Mammograms for Women Age 40-49, CNN Health (Nov. 16, 2009), [http://articles.cnn.com/2009-11-16/health/mammography.recommendation.changes\\_1\\_routine-mammograms-mammography-task-force?\\_s=PM:HEALTH](http://articles.cnn.com/2009-11-16/health/mammography.recommendation.changes_1_routine-mammograms-mammography-task-force?_s=PM:HEALTH). For more information on the task force and its projects, see U.S. Preventive Services Task Force, U.S. Dept. of Health & Human Serv., <http://www.ahrq.gov/clinic/uspstfix.htm> (last visited Dec. 29, 2011).

[FN21]. Daniel B. Klein & Alexander Tabarrok, Do Off-Label Drug Practices Argue Against FDA Efficacy Requirements? A Critical Analysis of Physicians' Argumentation for Initial Efficacy Requirements, 67 Am.

J. Econ. & Soc. 743, 744, 755 (2008). As observed by these authors, “Most cancer and AIDS patients are given drugs that are not FDA certified for the prescribed use. In a large number of fields, a majority of patients are prescribed at least one drug off-label.” *Id.* at 744 (citations omitted).

[FN22]. See Poling, *supra* note 3, at 119-20; Autism Spectrum Disorders: Treatment Options, Nat'l Inst. of Mental Health, <http://www.nimh.nih.gov/health/publications/autism/treatment-options.shtml> (last updated July 22, 2009). Off-label use is extremely pervasive in pediatrics, and data for the pharmaceutical treatment of behavior disorders in people with developmental disabilities is grossly insufficient. See Klein & Alexander, *supra* note 21, at 755; Poling, *supra* note 3, at 119-20.

[FN23]. Pub. L. No. 110-85, 121 Stat. 823 (codified as amended in scattered sections of 21 U.S.C.).

[FN24]. 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, 420, 434 (2010) [hereinafter *Evans, Seven Pillars*]. For a thorough discussion of the FDAAA, see *id.*, and 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) [hereinafter *Evans, Authority*].

[FN25]. See *Evans, Seven Pillars*, *supra* note 24, at 425.

[FN26]. For discussion of the impact of genetic science on drug development methodology and the associated potential to raise precision, see *infra* Part II.B.

[FN27]. See *supra* notes 8-9 and accompanying text.

[FN28]. Several guidances for clinical trials originally developed by the ICH have been adopted by the FDA and published in the Federal Register. See, e.g., International Conference on Harmonisation; Guidance on Statistical Principles for Clinical Trials, 63 *Fed. Reg.* 49,583 (Sept. 16, 1998); International Conference on Harmonization; Good Clinical Practice: Consolidated Guideline, 62 *Fed. Reg.* 25,692 (May 7, 1997); see generally *ICH Guidance Examines Statistical Principles to Support Clinical Research*, Guide to Good Clinical Prac. Newsl. (Thompson Publishing Group, Inc., Wash., D.C.), Nov. 1998, at 5, available at 6 No. 2 CLINPRAC-NWL 5 [hereinafter *ICH Guidance Examines*]. For general information about the ICH, visit its official website, <http://www.ich.org> (last visited Dec. 29, 2011).

[FN29]. See Cooper et al., *supra* note 7, at 201-24 (discussing a popular research method in applied behavior analysis); Johnston & Pennypacker, *Readings*, *supra* note 7, at 16-17; Johnston & Pennypacker, *Strategies and Tactics*, *supra* note 7, at 296-309.

[FN30]. R. Douglas Greer & Dolleen-Day Keohane, *A Real Science and Technology of Education*, in *Evidence-Based Educational Methods* 23, 37-38 (Daniel J. Moran & Richard W. Malott eds., 2004) [hereinafter *Greer & Keohane, Real Science*]; R. Douglas Greer et al., *The Effects of the Verbal Developmental Capability of Naming on How Children Can Be Taught*, 1 *Acta De Investigación*



Psicológica 23, 26-27 (2011); R. Douglas Greer & Dolleen-Day Keohane, The Evolution of Verbal Behavior in Children, *Behav. Dev. Bull.* 31 (2005), reprinted in 1 *J. Speech Language Pathology & Applied Behav. Analysis* 111, 112-13 (2006).

[FN31]. 45 C.F.R. §§ 46.401-409 (2010) (establishing children as one of the protected groups within overall human subject protection regulations). For discussion of the absence of children in drug development research, see *infra* notes 248-268.

[FN32]. See *supra* note 17.

[FN33]. See Greer & Keohane, *Real Science*, *supra* note 30, at 37-41.

[FN34]. See *supra* note 17; Poling, *supra* note 3, at 119.

[FN35]. Best Pharmaceuticals for Children Act, Pub. L. No. 107-109, 115 Stat. 1408 (2002) (codified as amended in scattered sections of 21 U.S.C. and 42 U.S.C.).

[FN36]. Orphan Drug Act, Pub. L. No. 97-414, § 2, 96 Stat. 2049, 2049-51 (1983) (codified as amended in scattered sections of 21 U.S.C. and 42 U.S.C.).

[FN37]. See *infra* notes 43-44, 92-94 and accompanying text.

[FN38]. Janosky et al., *supra* note 6, at 81.

[FN39]. Federal Food, Drug, and Cosmetic Act of 1938, Pub. L. No. 75-717, 52 Stat. 1040 (codified as amended at 21 U.S.C. §§ 301-399 (2006)) (“FDCA”). The FDCA has been amended more than 100 times. Peter Barton Hutt, A Historical Introduction, 45 *Food Drug Cosm. L.J.* 17 (1990), as reprinted in Peter Barton Hutt et al., *Food and Drug Law* 4 (3d ed. 2007). The Agency we now know as the FDA was created by the Federal Food and Drugs Act of 1906. Federal Food and Drugs Act of 1906, Pub. L. No. 59-384, 34 Stat. 768 (repealed 1938); John P. Swann, About FDA: FDA's Origins, *U.S. Food & Drug Admin.*, <http://www.fda.gov/AboutFDA/WhatWeDo/History/default.htm> (last visited Dec. 29, 2011). The Act prohibited adulterated and misbranded food and drugs and introduced an administrative enforcement clause to enable implementation. Paul Hyman, U.S. Food and Drug Law and FDA--A Historical Background, in *A Practical Guide to Food and Drug Law and Regulation* 21 (Kenneth R. Piña & Wayne L. Pines eds., 1st ed. 1998).

[FN40]. Richard A. Merrill, The Architecture of Government Regulation of Medical Products, 82 *Va. L. Rev.* 1753 (1996), as reprinted in Hutt et al., *supra* note 39, at 5.

[FN41]. Hutt et al., *supra* note 39, at viii.

[FN43]. *Id.* at 624; Janosky et al., *supra* note 6, at 81-82; Carey, *supra* note 6, at 77.

[FN44]. See generally ICH Guidance Examines, *supra* note 28; International Conference on Harmonisation; Guidance on Statistical Principles for Clinical Trials, 63 Fed. Reg. 49,583, 49,584 (Sept. 16, 1998). The ICH has developed shared scientific standards for clinical data and good clinical practice. Michael J. Malinowski, Ethics in a Global Biopharmaceutical Environment, 5 Santa Clara J. Int'l L. 57, 70-71 (2006), [http://www.scujil.org/sites/default/files/volumes/v5\\_MalinowskiArticle.pdf](http://www.scujil.org/sites/default/files/volumes/v5_MalinowskiArticle.pdf). For information about the ICH, visit its official website, <http://www.ich.org> (last visited Dec. 29, 2011). Six conferences have been held to date, and a seventh (the "ICH7 Conference") was scheduled to take place March 29-30, 2006, in Vienna, Austria, but was cancelled. ICH Steering Committee Meeting Summary 7 (June 5-8, 2006), available at [http://www.ich.org/uploads/media/SC\\_Report\\_Yokohama\\_2006.pdf](http://www.ich.org/uploads/media/SC_Report_Yokohama_2006.pdf). The organization itself, with representatives from both government and industry, operates in an ongoing manner. For an international extension of this Article that directly addresses the ICH, see Michael J. Malinowski & Grant G. Gautreaux, 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, 45 Cornell J. Int'l Law (forthcoming 2012).

[FN45]. Vision, ICH, <http://www.ich.org/about/vision.html> (last visited Dec. 29, 2011).

[FN46]. See International Conference on Harmonisation; Guidance on E15 Pharmacogenomics Definitions and Sample Coding, 73 Fed. Reg. 19,074 (Apr. 8, 2008).

[FN47]. *Id.* at 19,075. Pharmacogenomics and pharmacogenetics are defined and discussed *infra* at notes 48, 135, and 238 and accompanying text. In simplest terms, genomics is the science of genetic expression and its influence on human health. Genomics and Health, Ctrs. for Disease Control & Prevention, <http://www.cdc.gov/genomics/public/index.htm> (last updated Apr. 26, 2010). The discipline has become prevalent at the forefront of drug development, with completion of the map of the human genome announced in 2003. See *supra* note 13 and accompanying text. A biomarker is "[a] biochemical feature or facet that can be used to measure the progress of disease or the effects of treatment." Definition of Biomarker, MedicineNet, <http://www.medterms.com/script/main/art.asp?articlekey=6685> (last reviewed Apr. 27, 2011). The FDA provides a table of genomic biomarkers used in approved drug labels at Table of Pharmacogenomic Biomarkers in Drug Labels, U.S. Food & Drug Admin., <http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm> (last visited Dec. 29, 2011).

[FN48]. International Conference on Harmonisation; Guidance on E15 Pharmacogenomics Definitions and Sample Coding, 73 Fed. Reg. at 19,075.

[FN49]. Ctr. for Drug Evaluation and Research, U.S. Food & Drug Admin., Guidance for Industry: E16 Biomarkers Related to Drug or Biotechnology Product Development: Context, Structure, and Format of Qualification Submissions 1 & n.1, 2 (2011).

[FN50]. See *infra* notes 51-64 and accompanying text. Deviations from the standard drug approval clinical trial process described are granted for unusual circumstances, such as trials on drug candidates for very small patient disease groups and those for highly innovative therapeutics for presently untreatable conditions that will expose study participants to extremely high levels of risk. The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective, U.S. Food & Drug Admin., <http://www.fda.gov/drugs/resourcesforyou/consumers/ucm143534.htm> (last visited Dec. 29, 2011); see *infra* notes 268-69 and accompanying text; see also Risk and Responsibility: The Roles of FDA and Pharmaceutical Companies in Ensuring the Safety of Approved Drugs, Like Vioxx: Hearing Before the H. Comm. on Gov't Reform, 109th Cong. 24-25 (2005) (statement of Steven Galson, Acting Director Center for Drug Evaluation and Research) (outlining the pre-market approval process).

[FN51]. See 21 C.F.R. § 312.21(a) (2011).

[FN52]. Hutt et al., *supra* note 39, at 630-31.

[FN53]. 21 C.F.R. § 312.21(a).

[FN54]. *Id.* With an increase of innovative new drug candidates, Phase I trials have been modified in recent years to occasionally include efficacy testing in terminally ill patients particularly where there are nonexistent or insufficient existing treatments, thereby comingling traditional Phases I and II and clinical research and care. See Jamie L. Aldes, Note, The FDA Clinical Trial Process: Effectuating Chance in the Regulatory Framework Governing Clinical Trials to Account for the Historical Shift from “Traditional” to “New” Phase I Trials, 18 Health Matrix 463, 473-74 (2008).

[FN55]. Aldes, *supra* note 54, at 471.

[FN56]. 21 C.F.R. § 312.21(b) (2011).

[FN57]. *Id.* at § 312.21(c). Stuart R. Cohn & Erin M. Swick, The Sitting Ducks of Securities Class Action Litigation: Bio-Pharmas and the Need for Improved Evaluations of Scientific Data, 35 Del. J. Corp. L. 911, 918 (2010); Geoffrey M. Levitt, The Drugs/Biologics Approval Process, in A Practical Guide to Food and Drug Law and Regulation, *supra* note 39, at 101. As discussed *infra* at note 79 and in the accompanying text, over the last five years, typical Phase III trials have expanded from 5,000 to 20,000 subjects and their cost has doubled to surpass \$100 million. Nagano, *supra* note 1.

[FN58]. 21 C.F.R. § 314.126(a) (2010); Aldes, *supra* note 54, at 468. See generally W. John Thomas, The Vioxx Story: Would it have Ended Differently in the European Union?, 32 Am. J. L. & Med. 365 (2006) (discussing the approval of Vioxx under the American drug approval process and contrasting the U.S. approval process with that of the European Union).

[FN59]. See *supra* notes 19-22 and *infra* note 115-19 and accompanying text.

[FN60]. Aldes, *supra* note 54, at 472; see 21 C.F.R. § 314.80 (2011); Hutt et al., *supra* note 39, at 734-38.

[FN61]. Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, § 901, 121 Stat. 823, 922-43; Evans, *Seven Pillars*, *supra* note 24, at 477; see generally Evans, *Authority*, *supra* note 24; Malinowski & Gautreaux, *supra* note 44.

[FN62]. Post-marketing surveillance is sometimes referred to as “Phase V” trials. See Aldes, *supra* note 54, at 472 (“Phase V trials monitor the effects of the drugs as reported by physicians, survey data, and discover new uses for the drug.”).

[FN63]. See *Patient-Tailored Medicine Part Two*, *supra* note 13, at 16-17 (discussing lack of minority participants in clinical trials).

[FN64]. Office of Inspector Gen., U.S. Dep't of Health & Human Servs., *FDA's Monitoring of Postmarketing Study Commitments 1* (2006).

[FN65]. See Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, §130, 111 Stat. 2296, 2231-32 (codified at 21 U.S.C. 356b). Section 506B of FDAMA, the provision that promotes this presumption in favor of market approval, is codified under 21 U.S.C. § 356b. That same section provides FDA enforcement authority for 506B studies. 21 U.S.C. § 356b(d)-(e) (2006). See also Office of Inspector Gen., *supra* note 64, at 1, 2-3 (discussing 506B post-marketing studies).

[FN66]. Christopher D. Zalesky, *Considering Changes to CMS's National Coverage Decision Process: Applying Lessons Learned From FDA as a Regulator of Access to Healthcare Technology*, 57 *Food & Drug L.J.* 73, 86 (2002); James L. Zelenay, Jr., *The Prescription Drug User Fee Act: Is a Faster Food and Drug Administration Always a Better Food and Drug Administration?*, 60 *Food & Drug L.J.* 261, 295 (2005) (“PDUFA II [enacted in conjunction with FDAMA] shifted the agency's focus from one based solely on protecting the public from unsafe and ineffective products, possibly at the cost of expediency, to one that must balance this interest in safety with an interest in providing patients with speedy access to new drugs.”).

[FN67]. See U.S. Gov't Accountability Office, *GAO-06-402, Drug Safety: Improvement Needed in FDA's Postmarket Decision-making and Oversight Process 18-23* (2006) (finding the FDA lacks a clear and effective process for post-market drug safety decision making); Inst. of Med., *The Future of Drug Safety: Action Steps for Congress 1* (2006) (noting FDA's lack of clear authority to enforce compliance).

[FN68]. As explained under the ICH E9 Guidance, which incorporates FDA standards, exploratory trials “cannot be the basis of the formal proof of efficacy, although they may contribute to the total body of relevant evidence.” International Conference on Harmonisation; *Guidance on Statistical Principles for Clinical Trials*, 63 *Fed. Reg.* 49,583, 49,587 (Sept. 16, 1998). The Guidance “suggests that sponsors conducting confirmatory trials estimate the size of the effects of the investigational product and relate

the estimate to actual clinical significance. Because the hypothesis to be tested is largely based on clinical results and because a single confirmatory trial may be used to establish efficacy, adherence to the protocol and standard operating procedures is a must ....” ICH Guidance Examines, supra note 28.

[FN69]. Green, supra note 6, at 70-71.

[FN70]. See id. Testing against a placebo is testing against nothing, which is the extreme comparison--the greatest means to document efficacy data in patient group research. See id.

[FN71]. International Conference on Harmonisation; Guidance on Statistical Principles for Clinical Trials, 63 Fed. Reg. at 49,587. The E9 Guidance recommends using double-blinding where investigational “treatments are prepacked with a randomization schedule, and supplied to the trial center(s) labeled only with the subject number and the treatment period so that no one involved in the conduct of the trial is aware of the specific treatment allocated to any particular subject.” Id. According to the Guidance, blind breaking should only occur when the trial subject's physician deems it necessary; if blind breaking does occur, it “should be reported and explained at the end of the trial.” Id. A trend increasing in recent years is for study participants to use modern technology to remove their half of the double-blind--from internet access to communication with other subjects via patient group chat rooms and blogs that enable collective information and comparisons, to sending blood samples to independent laboratories to discern directly whether they are getting the drug candidate. Lawrence M. Friedman et al., *Fundamentals of Clinical Trials* 87 (3d ed. 1996).

[FN72]. Ethics norms for domestic U.S. research, as embodied in the Common Rule, ban denial of access to existing treatments with instances of seriously debilitating and life-threatening conditions. See Paul Litton & Franklin G. Miller, A Normative Justification for Distinguishing the Ethics of Clinical Research from the Ethics of Medical Care, 33 *J.L. Med. & Ethics* 566, 570 (2005) (“[U]nder the seven principles for research, it would be unethical to withhold effective treatment to such ill persons for research purposes if withholding treatment exposes a person to grave risk.”). For the same reason, once data establishes efficacy and safety during a trial to develop treatments for such conditions, study sponsors typically must make the drug candidate available to all of those in its trials. Id.

[FN73]. See supra note 72 and accompanying text.

[FN74]. 21 C.F.R. § 314.510 (2010). The ICH E9 Guidance suggests that,

In choosing which clinical endpoints to test for, the guidance recommends that sponsors select primary endpoints capable of providing the most clinically relevant and convincing evidence directly related to the trial's main objective. Typically, there should be but one primary endpoint. Usually, efficacy should be the primary endpoint, although safety, tolerability, or quality-of-life measurements also may serve as the foremost endpoints to be tested, the guidance states.

ICH Guidance Examines, *supra* note 28. The FDA has been criticized for accepting surrogate endpoints for accelerated, conditional market approval and then failing to enforce follow-on study requirements. U.S. Gov't Accountability Office, GAO-09-866, *New Drug Approval: FDA Needs to Enhance Its Oversight of Drugs Approved on the Basis of Surrogate Endpoints* 29 (2009). According to the GAO, the FDA has required over 144 studies since introducing the accelerated approval program in 1992. *Id.* at 18. More than a third of those are still pending and the Agency never has pulled a drug for failure to conduct long-term studies. *Id.* at 18, 29. The FDA does not routinely check whether companies are making progress on required studies. *Id.* at 29-32.

[FN75]. See *supra* notes 10, 17 and accompanying text (explaining the use of averages in GD statistics).

[FN76]. This point is illustrated in a discussion of the tremendous genetic diversity associated with the health care condition categorized as “dwarfism.” See Michael J. Malinowski, *Dealing with the Realities of Race and Ethnicity: A Bioethics-Centered Argument in Favor of Race-Based Genetics Research*, 45 *Hous. L. Rev.* 1415, 1451-57 (2009) (profiling the Roloff family from the television show “Little People, Big World” as a case study).

[FN77]. Janosky et al., *supra* note 6, at 81-82 (footnotes omitted). The renowned Dr. Jerome Groopman has reached the same conclusion: “Statistics cannot substitute for the human being before you; statistics embody averages, not individuals. Numbers can only complement a physician's personal experience with a drug or a procedure, as well as his knowledge of whether a ‘best’ therapy from a clinical trial fits a patient's particular needs and values.” Jerome Groopman, *How Doctors Think* 6 (2007). Similarly, as observed by another commentator:

The best way to go from intuition to evidence is the randomized clinical trial. Patients with a particular condition are randomly assigned to competing treatments or, if appropriate, to a placebo. By monitoring the patients for months or years, doctors learn the relative risks and benefits of the treatment being studied.

But such trials take years and cost many millions of dollars. By the time the results come in, science and medicine may have moved on, making the findings less relevant. Moreover, patients in a clinical trial usually aren't representative of real people, who tend to have complex combinations of diseases and medical problems. And patients often don't stick with the program.

Carey, *supra* note 6, at 77 (emphasis added).

[FN78]. Nagano, *supra* note 1.

[FN80]. *Id.* In addition to the speed of subject recruitment (the primary driver for expansion of recruitment outside of the United States),

To seek bigger patient pools, most major CROs have expanded operations overseas to India, Russia, Latin America, Eastern Europe and other emerging markets. U.S.-based CROs have a presence in more than 70 countries.

In those countries, CROs can easily find a large number of “treatment-naïve patients” who aren't taking other drugs and are thus the best candidates for trials.

*Id.*

[FN81]. Ctr. for Health & Pharm. Law & Policy, Seton Hall Law, White Paper: Conflicts of Interest in Clinical Trial Recruitment & Enrollment: A Call for Increased Oversight 5 (2009).

[FN82]. See *infra* Part II.

[FN83]. See *supra* notes 23-25 and accompanying text.

[FN84]. Gardiner Harris, A New Federal Research Center Will Help to Develop Medicines, *N.Y. Times*, Jan. 23, 2011, at A1.

[FN85]. See *supra* note 7 and accompanying text. For detailed discussion of the SSRD methodology, see Janosky et al., *supra* note 6, at 25-43.

[FN86]. Janosky et al., *supra* note 6, at 81; see also *id.* at 81-96 (discussing direct application of SSRD in biomedicine).

[FN87]. Poling et al., *supra* note 3, at 119.

[FN88]. Janosky et al., *supra* note 6, at 82.

[FN89]. Green, *supra* note 6, at 74. “In a single-case experiment, each data point represents one of the repeated direct measurements of the target behavior, as opposed to a mathematical abstract like a group mean test score. Graphing those data provides a picture of exactly how behavior unfolds in real time under specific conditions.” *Id.* at 78.

[FN90]. *Id.* at 74. For an overview on SSRD methodology, see Blampied Presentation, *supra* note 7.

[FN91]. Green, *supra* note 6, at 78-79.

[FN93]. *Id.*

[FN94]. *Id.*

[FN95]. *Id.*

[FN96]. Patient-Tailored Medicine Part One, *supra* note 13, at 9.

[FN97]. See Green, *supra* note 6, at 73. As explained by Professor Green, “[l]ike other scientists, behavior analysts have devised research methods that are suited to their particular subject matter, while meeting all of the general requirements of science.” *Id.* at 73. These requirements include careful observation, objective measurement, controlled experiments, analysis and interpretation of data, and repetition (replication) of experiments. *Id.* at 70. Because the focus is on individual behavior unfolding over time, single-case research designs are used for most behavior analytic studies. These are true experiments, not “case studies” or nonexperimental observational studies. *Id.* at 74.

[FN98]. Janosky et al., *supra* note 6, at 28 (citations omitted). R.A. Fisher introduced the first official single subject clinical trial experimental paradigm in 1945. *Id.* at 1.

[FN99]. See *supra* note 33 and accompanying text.

[FN100]. See *supra* note 33 and accompanying text.

[FN101]. See Greer & Keohane, *Real Science*, *supra* note 30, at 37-38.

[FN102]. See R. Douglas Greer, *Designing Teaching Strategies: An Applied Behavior Analysis Approach* 161-163 (2002).

[FN103]. Joe Levine, *The Unorthodox Behaviorist*, *TC Today*, Spring 2007, at 24, 26-27.

[FN104]. Poling et al., *supra* note 3, at 119.

[FN105]. Marcia Angell, *The Truth About the Drug Companies*, at xv (2004).

[FN106]. See Paul Starr, *The Social Transformation of American Medicine*, 336-37 (1982) (detailing a growing dependence on pharmaceuticals and medical technology following World War I).

[FN107]. See, e.g., *id.* at 335-36 (noting, for example, advances in antibiotics and Malaria control).

[FN108]. Jürgen Drews, *Drug Discovery: A Historical Perspective*, 287 *Sci.* 1960, 1962 (2000); Michael J. Malinowski, *Respecting, Rather than Reacting to, Race in Basic Biomedical Research: A Response to*



Professors Caulfield and Mwaria, 45 Hous. L. Rev. 1489, 1492 n.16 (2009); Thomas Reiss, Drug Discovery of the Future: The Implications of the Human Genome Project, 19 Trends Biotechnology 496, 496 (2001). “This surprisingly low number of targets illustrates that the identification of clinically relevant and interesting targets was the primary bottleneck of the drug discovery process.” Patient-Tailored Medicine Part One, *supra* note 13, at 12.

[FN109]. Drug Discovery and Development, PhRMA, [http:// www.Pharma.org/research/drug-discovery-development](http://www.Pharma.org/research/drug-discovery-development) (last visited Dec. 29, 2011).

[FN110]. See Evans, Seven Pillars, *supra* note 24, at 439-44 (discussing efficacy as the purpose of randomized, controlled clinical trials).

[FN111]. Patient-Tailored Medicine Part One, *supra* note 13, at 11-12 (citing Press Release, Tufts Ctr. for the Study of Drug Dev., Background: How New Drugs Move Through the Development and Approval Process (Nov. 2001), available at [http://csdd.tufts.edu/files/uploads/how\\_new\\_drugs\\_move.pdf](http://csdd.tufts.edu/files/uploads/how_new_drugs_move.pdf)); see generally Jim Gilbert et al., Rebuilding Big Pharma's Business Model, *In Vivo: Bus. & Med. Rep.*, Nov. 2003, at 73 (2003), available at [www.bain.com/bainweb/PDFs/cms/Marketing/rebuilding\\_big\\_pharma.pdf](http://www.bain.com/bainweb/PDFs/cms/Marketing/rebuilding_big_pharma.pdf) (outlining the traditional methods that have led the drug industry to profit loss, including a random, all-inclusive, expensive testing process).

[FN112]. See *supra* notes 19-22 and accompanying text.

[FN113]. Thomas, *supra* note 58, at 372; Patient-Tailored Medicine Part One, *supra* note 13, at 24; Harris Meyer, Costly Stamp of Approval, *L.A. Times*, Jan. 18, 2010, at E3. Sponsors have been required to demonstrate safety since 1938. *Id.*

[FN114]. Patient-Tailored Medicine Part One, *supra* note 13, at 9 (“Nonetheless, not until the second half of the twentieth century has much attention been paid to drug safety and, even then, adverse drug reactions were considered part of the practice of medicine.”); David Classen, Medication Safety: Moving from Illusion to Reality, 289 *JAMA* 1154, 1154 (2003); Evans, Seven Pillars, *supra* note 24, at 449.

[FN115]. See *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 350 (2001); *Wash. Legal Found. v. Henney*, 202 F.3d 331, 333 (D.C. Cir. 2000) (calling off-label use “commonplace”); *Wash. Legal Found. v. Friedman*, 13 F. Supp. 2d 51, 56 (D.D.C. 1998), vacated in part on other grounds *sub nom.* *Wash. Legal Found. v. Henney*, 202 F.3d 331 (D.C. Cir. 2000) (observing that “off-label use of FDA-approved drugs by physicians is an established aspect of the modern practice of medicine”).

[FN116]. *Pharm. Researchers & Mfrs. of Am.*, *Pharmaceutical Industry Profile* 26 fig.8 (2010); see *Ctr. for Health & Pharm. Law & Policy*, *supra* note 81, at 9 (calling the cost of “nontreatment activities,” including research, considerable and substantial).

[FN117]. Angell, *supra* note 105, at 11-12. The FDA has estimated that almost two percent of all prescription drugs--thousands of medicines that include powerful active ingredients such as antihistamines, narcotics and sedatives-- are marketed illegally without its approval. Meyer, *supra* note 113.

[FN118]. Meyer, *supra* note 113 (explaining that high prices of FDA-approved drugs leads to use of cheaper, unapproved off-label drugs).

[FN119]. Angell, *supra* note 105, at 123-26 (describing how direct-to-consumer advertising both persuades and misleads consumers).

[FN120]. See Inst. of Med., *supra* note 67, at 2 (suggesting black triangle indicators for new drug approvals to flag the lack of market history); Wylie Burke & Bruce M. Psaty, Personalized Medicine in the Era of Genomics, 298 JAMA 1682, 1682-84 (2007) (detailing the potential of experimental, genetically personalized pharmaceutical treatment).

[FN121]. Patient-Tailored Medicine Part One, *supra* note 13, at 9, 16-17; see also Inst. of Med., *The Future of Drug Safety: Promoting and Protecting the Health of the Public* 54 box2-5 (2007) (relating drug-specific data on adverse effects as reported to the FDA).

To 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. Nonetheless, not until the second half of the twentieth century has much attention been paid to drug safety and, even then, adverse drug reactions were considered part of the practice of medicine.

Today, because adverse drug reactions cause more than two million hospitalizations and 100,000 deaths annually in the United States, there are strong clinical, economic, and ethical imperatives to address the manifold causes of these numbers.

Patient-Tailored Medicine Part One, *supra* note 13, at 9 (footnotes omitted). See also BS Shastri, Pharmacogenetics and the Concept of Individualized Medicine, 6 *Pharmacogenomics J.* 16, 16 (2006). Negative outcomes may result both from errors in prescribing and dispensing and from individuals' adverse reactions to the drugs themselves. Petra A. Thürmann, Prescribing Errors Resulting in Adverse Drug Events: How Can They Be Prevented?, 5 *Expert Opinion on Drug Safety* 489, 490 (2006). It is entirely possible that one of the causes of adverse drug reactions is the method by which individual patients metabolize those drugs. Kathryn A. Phillips et al., Potential Role of Pharmacogenomics in Reducing Adverse Drug Reactions: A Systematic Review, 286 *JAMA* 2270, 2270 (2001).

[FN122]. Shastri, *supra* note 121, at 16. One 2005 report stated that approximately 40,000 people are killed in automobile accidents every year. Miranda Hitti, Car Crashes Kill 40,000 in U.S. Every Year, Fox

News (Feb. 3, 2005), <http://www.foxnews.com/story/0,2933,146212,00.html>.

[FN123]. Carey, *supra* note 6, at 73 (reporting on the movement for evidence-based medicine).

[FN124]. See generally Starr, *supra* note 106.

[FN125]. See generally Genomics Revolution, *supra* note 13; Nagano, *supra* note 1 (“The consensus on Wall Street: Big Pharma's business model is ‘broken, and no longer working’ ....”).

[FN126]. See Press Release, U.S. Food & Drug Admin., FDA Completes Final Phase of Planning for Consolidation of Certain Products from CBER to CDER, (Mar. 17, 2003), available at <http://www.scienceblog.com/community/older/archives/M/2/fda1387.htm>. Until 2004, biologic drugs were reviewed by the Center for Biologics Evaluation and Research. Transfer of Therapeutic Products to the Center for Drug Evaluation and Research, U.S. Food & Drug Admin., <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/ucm133463.htm> (last visited Dec. 29, 2011). Where the drugs were a combination of traditional and biotech, sponsors had some choice in where to file for review. Influenced by the trend of biopharmaceuticals, all drug review and the relevant resources were centralized in CDER. *Id.*

[FN127]. See Transfer of Therapeutic Products, *supra* note 126.

[FN128]. See Press Release, Nat'l Human Genome Research Inst., International Consortium Completes Human Genome Project, (Apr. 14, 2003), available at <http://www.genome.gov/11006929> [hereinafter International Consortium]. The Human Genome Project (“HGP”), commenced in 1990, was undertaken to identify and map the sequence of information coded in DNA and to identify active human genes--segments of DNA. *Id.*; Patient-Tailored Medicine Part One, *supra* note 13, at 10-11. A rough map of the human genome was completed in 2003, years ahead of schedule. Patient-Tailored Medicine Part One, *supra* note 13, at 11. Information about the HGP may be obtained from the National Human Genome Research Institute (“NHGRI”) at [www.nhgri.nih.gov/HGP](http://www.nhgri.nih.gov/HGP). For more information on the human genome generally, see the February 16, 2001 issue of Science entitled “The Human Genome,” 291 Sci. 1145 (2001) and the February 15, 2001 Issue of Nature, 409 Nature 745 (2001), also entitled “The Human Genome” dedicated to a draft of the map of the human genome. See also Subcomm. on Human Genome of the Health & Env'tl. Research Advisory Comm. for the U.S. Dep't of Energy, Report on the Human Genome Initiative for the Office of Environmental Research (1987), available at [www.ornl.gov/sci/techresources/Human\\_Genome/project/herac2.shtml](http://www.ornl.gov/sci/techresources/Human_Genome/project/herac2.shtml) (discussing the need for and value of a map of human DNA); Eric S. Lander, Scientific Commentary: The Scientific Foundations and Medical and Social Prospects of the Human Genome Project, 26 J.L. Med. & Ethics 184, 184 (1998) (explaining the HGP and the possibilities that arise with unlocking the “human periodic table”). Once genes are identified, comparisons can be made among individuals to identify genetic variations and assess their function and impact on human health. See Ctr. for Genetics Educ., The Human Genetic Code--The Human Genome Project and Beyond (2007), available at [www.genetics.com.au/pdf/factsheets/fs24.pdf](http://www.genetics.com.au/pdf/factsheets/fs24.pdf) (noting diagnosis and predictive testing for genetic

conditions).

[FN129]. See Press Release, Nat'l Human Genome Research Inst., International Consortium Announces the 1000 Genomes Project (Jan. 22, 2008), available at <http://www.1000genomes.org/sites/1000genomes.org/files/docs/1000genomes-newsrelease.pdf>.

An international research consortium today announced the 1000 Genomes Project, an ambitious effort that will involve sequencing the genomes of at least a thousand people from around the world to create the most detailed and medically useful picture to date of human genetic variation. The project will receive major support from the Wellcome Trust Sanger Institute in Hinxton, England, the Beijing Genomics Institute, Shenzhen (BGI Shenzhen) in China and the National Human Genome Research Institute (NHGRI), part of the National Institutes of Health (NIH).

Id.

[FN130]. Peter Imming et al., *Drugs, Their Targets and the Nature and Number of Drug Targets*, 5 *Nature Reviews: Drug Discovery* 821, 830 (2006). A drug target is “a molecular structure (chemically definable by at least a molecular mass) that will undergo a specific interaction with chemicals that we call drugs because they are administered to treat or diagnose a disease. The interaction has a connection with the clinical effect(s).” *Id.* at 821.

[FN131]. See *supra* note 13 for a discussion of epigenetics.

[FN132]. See Biotechnology Indus. Org., *Guide to Biotechnology 2008* 32-40 (2008), available at <http://www.bio.org/node/2801> (discussing some of the therapies made possible by recent research advances).

[FN133]. *Patient-Tailored Medicine Part One*, *supra* note 13, at 11.

[FN134]. William E. Evans & Mary V. Relling, *Moving Towards Individualized Medicine With Pharmacogenics*, 429 *Nature* 464, 466, 468 (2004). More than 3 million human genetic variations, called single nucleotide polymorphisms (“SNPS”), had been identified by April 2003. International Consortium, *supra* note 128.

[FN135]. In simplest terms, pharmacogenomics utilizes genetic profiling in pharmacology--for example, centering a human clinical trial on members of a disease group under study who share a particular genetic variation. When successful, the result is associations between specific human genetic variations and responsiveness to pharmaceuticals, thereby enabling individualized medicine based on genetic profiling, which is a field known as pharmacogenetics. See *supra* notes 46-47 and accompanying text. Complementary fields are pharmacogenomics, which is research centered on the expression of alleles shared by groups, and pharmacogenetics, the tailoring of health care and biopharmaceuticals to individual genetic profiles. See Malinowski, *supra* note 13, at 32; Noah, *supra* note 13, 7-11; Janet

Woodcock, FDA Policy on Pharmacogenomic Data in Drug Development, 66 La. L. Rev. 91, 92 (2005).

[FN136]. See Patient-Tailored Medicine Part One, *supra* note 13, at 6-7; Burke & Psaty, *supra* note 120, at 1684; Susan B. Shurin & Elizabeth G. Nabel, Pharmacogenomics--Ready for Prime Time?, 358 New Eng. J. Med. 1061, 1062-63 (2008). "Biotechnology also has created a wave of new genetic tests. Today there are more than 1,200 such tests in clinical use, according to genetests.org, a site sponsored by the University of Washington. Many are for genetic diseases, while others test predisposition to disease. Emerging applications include tests to predict response to medicines and assist with nutritional planning." Biotechnology Indus. Org., *supra* note 132, at 32.

[FN137]. Patient-Tailored Medicine Part One, *supra* note 13, at 12. See also The Int'l SNP Map Working Grp., A Map of Human Genome Sequence Variation Containing 1.42 Million Single Nucleotide Polymorphisms, 409 Nature 928, 932 (2001) (discussing the various benefits anticipated from the human genome map).

[FN138]. See generally Robert Bazell, Her-2: The Making of Herceptin, a Revolutionary Treatment for Breast Cancer (1998).

[FN139]. Brian J. Druker, STI571 (Gleevec™) as a Paradigm for Cancer Therapy, 8 Trends Molecular Med. S14, S14 (2002).

[FN140]. Steven Reinberg, New Cancer Drug Fights Tumors in Those with BRCA Mutations, U.S. News & World Rep. (June 24, 2009), <http://health.usnews.com/articles/health/healthday/2009/06/24/new-cancer-drug-fights-tumors-in-those-with-brca.html>.

[FN141]. See Angell, *supra* note 105, at xv-xvii; U.S. Food & Drug Admin., Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products (2004), available at <http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/CriticalPathInitiative/CriticalPathOpportunitiesReports/ucm113411.pdf> (providing a comprehensive discussion on the challenges facing biopharmaceuticals, despite recent advances in biomedical research, as well as potential solutions); Bitter Medicine: Pills, Profit, and the Public Health (ABC News television broadcast May 29, 2002).

[FN142]. Nicholas Wade, A Decade Later, Gene Map Yields Few New Cures, N.Y. Times, June 13, 2010, at A1.

[FN143]. See Patient-Tailored Medicine Part One, *supra* note 13, at 35.

[FN144]. See *supra* notes 1-3 and accompanying text.

[FN145]. Pharm. Researchers & Mfrs. of Am., *supra* note 116, at iii.

[FN146]. Jared A. Favole & Jennifer Corbett Dooren, FDA Approved More Drugs in 2008, Wall St. J., Jan.

2, 2009, at A9; New Drug Approvals on Pace to Exceed 2008 Total, *supra* note 1; Silverman, *supra* note 1; see also Jenna Greene, Has Obama Redirected the Regulatory System?, *Nat'l L. J.*, Jan. 18, 2010, at 11 (noting that the number of FDA approvals under the Obama administration are “on par or even more accommodating than” the Bush Administration); Pete Harpum, Articulating a Vision for Best Practice Project Management in Drug Development, *PM World Today*, Oct. 2008, at 1, <http://www.pmforum.org/library/papers/2008/PDFs/Harpum-10-08.pdf>.

[FN147]. See Asher Mullard, 2010 FDA Drug Approvals, 10 *Nature Revs.: Drug Discovery* 82, 84 tbl.1 (2011) (listing CDER's approvals in 2010 in chart form).

[FN148]. FDA's Drug Approvals Flat 2009, Safety Up, MSNBC (Jan. 5, 2010, 1:37 PM), [http://www.msnbc.msn.com/id/34708085/ns/health-health\\_care/t/fdas-drug-approvals-flat-safety/](http://www.msnbc.msn.com/id/34708085/ns/health-health_care/t/fdas-drug-approvals-flat-safety/).

[FN149]. Harris, *supra* note 2.

[FN150]. *Id.*

[FN151]. *Id.*

[FN152]. *Ctr. for Health & Pharm. Law & Policy*, *supra* note 81, at 6.

[FN153]. Nagano, *supra* note 1.

[FN154]. *Ctr. for Health & Pharm. Law & Policy*, *supra* note 81, at 5.

[FN155]. Nagano, *supra* note 1.

[FN156]. See U.S. Gov't Accountability Office, *supra* note 67; *Inst. of Med.*, *supra* note 67.

[FN157]. Thomas, *supra* note 58, at 371-73.

[FN158]. Gina Kolata, When Drugs Cause Problems They Are Supposed to Prevent, *N.Y. Times*, Oct. 17, 2010, at A18.

[FN159]. *Id.*

[FN160]. *Id.* The recent Avandia controversy triggered an expansive U.S. Senate Finance Committee inquiry and bipartisan report highly critical of both GlaxoSmithKline (“GSK”) and the FDA. See Staff of S. Comm. on Finance, 111th Cong., Rep. on GlaxoSmithKline and the Diabetes Drug Avandia 1 (Comm. Print. 2010) [hereinafter Report on Avandia]. This medication, introduced to the market in 1999 and prescribed to hundreds of thousands of patients annually to treat type 2 diabetes, caused 83,000 heart attacks between 1999 and 2007, according to the FDA's own estimates. *Id.* at 1-4; Gardiner Harris,

Research Ties Diabetes Drug to Heart Woes, N.Y. Times, Feb. 20, 2010, at A1. GSK researchers identified a link between Avandia and serious heart disease in 2004, 2005, and 2006, the FDA issued a warning in 2007, the FDA's top officials in the Office of Surveillance and Epidemiology recommended a full market recall, and internal FDA reports indicated that switching Avandia patients to an alternative drug could prevent about 500 heart attacks and 300 cases of heart failure each month. Report on Avandia, *supra*, at 14, 93; Harris, *supra*. According to the Senate Report, executives at the pharmaceutical company “attempted to intimidate independent physicians, focused on strategies to minimize or misrepresent findings that Avandia may increase cardiovascular risk, and sought ways to downplay findings that a competing drug might reduce cardiovascular risk.” Report on Avandia, *supra*, at 1. GSK responded by challenging the report and defending Avandia. *Id.* at 8. Although GSK is undertaking another round of clinical trials to research the increased risk of heart disease, those are not projected to be completed until 2020. Harris, *supra*. Many lawmakers, consumer advocates, and other stakeholders are calling for regulatory reform of the FDA to grant officials in the Office of Surveillance and Epidemiology independent decision-making power on par with that of officials who approve drugs. Alyah Khan, Recent Avandia Report Sparks Concerns Over Internal FDA Power Struggle, *FDA Wk.*, Feb. 26, 2010, at 4, 4. This suggestion was made years earlier, including in the 2006 Institute of Medicine's Report on the FDA and in the law literature. *Inst. of Med.*, *supra* note 67, at 1, 3; see Thomas, *supra* note 58, at 379.

[FN161]. Kolata, *supra* note 158.

[FN162]. Steven Bushong, Accutane Off Shelves, but Lawsuits Live, *Columbus Dispatch*, July 3, 2009, at A1; Accutane Side Effects, *Drug Watch*, <http://www.drugwatch.com/accutane/side-effects.php> (last modified Sept. 30, 2011).

[FN163]. Accutane Side Effects, *supra* note 162; Press Release, Roche Pharmaceuticals, Roche Discontinues and Plans to Delist Accutane in the U.S. (June 29, 2009), available at <http://www.rocheusa.com/portal/synergy/static/file/synergy/alfproxy/download/1414-cd2ddc12b4d211deadd62f6357bc6b3c/last/roche%20discontinues%20and%20plans%20to%20delist%20accutane%20in%20the%u.s..pdf>.

[FN164]. For a thoughtful argument of over-regulation, see Richard A. Epstein, *Overdose: How Excessive Government Regulation Stifles Pharmaceutical Innovation* (2006). Note, however, that Professor Epstein does not directly address or challenge the core proposal of this Article--changing the core science standard in the context of the existing regulatory infrastructure.

[FN165]. See Angell, *supra* note 105, at 7-10, 13-17.

The culture within the FDA, [is] one where the pharmaceutical industry, which the FDA is supposed to regulate, is seen by the FDA as its client instead.” The lack of adequate regulation of the pharmaceutical industry by the FDA has led to many deaths and recalls of unsafe drugs, such as Vioxx, that the FDA had approved for public use [in 1999]. As Sen. Charles Grassley (R-Iowa) explained, “[c]onsumers should not have to second-guess the safety of what's in their medicine cabinet.” Unfortunately, many consumers

suffer as a result of the current ineffective state of the FDA's regulatory framework governing the drug testing and approval process.

Aldes, *supra* note 54, at 463 (footnotes omitted).

[FN166]. For an excellent treatment of the Vioxx controversy with a focus on the overall U.S. and EU regulatory processes for pharmaceuticals, see Thomas, *supra* note 58. Vioxx illustrates all too vividly that, without meaningful regulatory reform, it may take many years of market use; tremendous financial costs to consumers, taxpayers, and other payers; lost opportunities to improve human health; and even the loss of many human lives before serious product shortcomings are confronted. In a 2002 broadcast journalism documentary entitled *Bitter Medicine: Pills, Profit, and the Public Health*, *supra* note 141, Vioxx was challenged on many levels—several years before its market recall. Nevertheless, the product remained on the market at tremendous cost above over-the-counter alternatives such as Ibuprofen, only to be exposed and pulled from the market in 2004. Thomas, *supra* note 58, at 366, 368.

[FN167]. Nagano, *supra* note 1. CROs are commercial service providers that meet both basic and clinical research needs, and the business is burgeoning. *Id.* Unfortunately, guidance and enforceable law-policy to protect human subjects has not been introduced in sync with this trend:

The globalization of medical research is, in effect, quickly outpacing the development of internationally accepted ethical guidelines for the conduct of research. For many medical researchers working in resource-poor countries, ethical decision-making is like sailing in the days before modern navigation; one is never quite sure where one is, or in what direction one is headed.

Daniel W. Fitzgerald & Angela Wasunna, *Away from Exploitation and Towards Engagement: An Ethical Compass for Medical Researchers Working in Resource-Poor Countries*, 33 *J.L. Med. & Ethics* 559, 559 (2005); see also Malinowski, *supra* note 44, at 70-71 (offering several options for dealing with the gap); Jennifer L. Gold & David M. Studdert, *Clinical Trials Registries: A Reform That Is Past Due*, 33 *J.L. Med. & Ethics* 811, 811 (2005) (supporting the establishment of a conclusive registry for clinical trials conducted abroad); Joe Stephens, *Where Profits and Lives Hang in Balance*, *Wash. Post*, Dec. 17, 2000, at A1 (discussing the lack of regulation and oversight characteristic of trials in some foreign countries).

A sign of the trend: In August, Princeton, N.J.-based CovanceCVD, the largest U.S. CRO, struck a deal with Eli Lilly to buy Lilly's R&D labs in Indiana for \$50 million. The deal will transfer 260 Lilly employees to Covance. Lilly also guaranteed Covance a 10-year business contract worth \$1.6 billion.

Nagano, *supra* note 1.

[FN168]. Both the GAO and IOM have criticized the FDA's performance regulating new drugs in the marketplace and emphasized the need to make the clinical research data submitted for market approval transparent to the public. U.S. Gov't Accountability Office, *supra* note 67, at 5; *Inst. of Med.*, *supra* note 67, at 3. Neither Congress nor the FDA have addressed the possibility that the drop-off in innovative



new drug approvals and poor performance of many on the market are an indication that the integrity of the entire forthcoming generation of biopharmaceuticals has been jeopardized by law and policy that comprehensively integrated academia and industry without shoring up the public nature of science. Michael J. Malinowski, Keynote Address: A Discourse on the Public Nature of Research in Contemporary Life Science: A Law-Policy Proposal to Promote the Public Nature of Science in an Era of Academia-Industry Integration, in *Biennial Review of Law, Science & Technology* 1, 9-12 (2010). During the span of the career of a single academic researcher, norms have shifted from industry independence, collegiality, disclosure and sharing of materials and information, quick and unfettered publication, and broad dissemination of information that invited meaningful scrutiny and rigorous peer review to strong technology transfer administration within academic research institutions, no communication without executed confidentiality and disclosure agreements and provisional patent applications, no publication without sponsor preapproval, and no sharing of materials without executed material transfer agreements. See *id.* at 9-19.

[FN169]. Press Release, U.S. Food & Drug Admin., FDA Forms Transparency Task Force (June 2, 2009), available at <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm163899.htm>. In 2004, Congress considered measures to force public disclosure of clinical data through the Internet to enable scrutiny by the medical and science communities, but then backed away when some of the major pharmaceutical companies announced they would do so voluntarily. See Ted Agres, *Congress Wants Data to Be Free*, *Drug Discovery & Dev.*, Nov. 2004, at 14; Editorial, *Hiding the Data on Drug Trials*, *N.Y. Times*, June 1, 2005, at A20 (commenting on a government survey that “determined that three of the largest drug companies [Merck, GlaxoSmithKline, and Pfizer] have effectively reneged on their pledges to list trials in a federal database”); Tamsin Waghorn, *Rattled Drug Giants Act Over Safety Concerns*, *Express*, Jan. 7, 2005, at 78.

[FN170]. See Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, § 130, 111 Stat. 2296, 2231-32 (codified at 21 U.S.C. 356b; 21 U.S.C. § 355a (2006)). The Agency's mission was expanded from ensuring efficacy and safety to including efficiency. See *supra* note 66 and accompanying text.

[FN171]. Prescription Drug User Fee Act of 1992, Pub. L. No. 102-571, 106 Stat. 4491 (codified primarily at 21 U.S.C. § 379g-h). PDUFA, which was enacted with a five year sunset provision, has been reauthorized three times. See *supra* note 66 (PDUFA II enacted in conjunction with FDAMA in 1997); Public Health Security and Bioterrorism Preparedness and Response Act of 2002, Pub. L. No. 107-188, §§ 501-509, 116 Stat. 594, 687-694 (PDUFA III); Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, §§ 101-109, 121 Stat. 823, 825-842 (codified as amended in scattered sections of 21 U.S.C.) (authorizing PDUFA IV through 2012).

[FN172]. Food and Drug Administration Modernization Act of 1997, 111 Stat. 2296.

[FN173]. Evans, *Seven Pillars*, *supra* note 24, at 454 n.240, 478, 486.

[FN174]. U.S. Gov't Accountability Office, *supra* note 74, at 15. For a critique of the FDA's post-market decision-making process, see U.S. Gov't Accountability Office, *supra* note 67.

[FN175]. U.S. Gov't Accountability Office, *supra* note 74, at 32-33.

[FN176]. *Id.* at 33. For example, Shire Laboratories failed to complete a study for ProAmatine, a medication for low blood pressure, for more than thirteen years. *Id.* at 33-34.

[FN177]. U.S. Gov't Accountability Office, *supra* note 67, at 18-36; Inst. of Med., *supra* note 67, at 1.

[FN178]. Malinowski, *supra* note 168, at 23.

[FN179]. *Id.* at 13-19.

[FN180]. Lorelei Ritchie de Larena, *The Price of Progress: Are Universities Adding to the Cost?*, 43 *Hous. L. Rev.* 1373, 1375 (2007). For another evaluation of the Bayh-Dole Act, which gave universities greater patent rights, see David C. Mowery et al., *Ivory Tower and Industrial Innovation: University-Industry Technology Transfer Before and After the Bayh-Dole Act* (2004).

[FN181]. Malinowski, *supra* note 168, at 16. Several of the most renowned science publications, including the *New England Journal of Medicine* and *Journal of the American Medical Association* ("JAMA"), have been involved in embarrassing conflicts of interest controversies. See Linda A. Johnson, *New England Journal of Medicine Admits Lapses in Ethics Policy*, *Chi. Sun-Times*, Feb. 24, 2000, at 21 (reporting that the "New England Journal of Medicine admitted violating its financial conflict-of-interest policy 19 times over the last three years in its selection of doctors to review new drug treatments").

The primary guidance for conflict of interest management by medical journals is the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, a consensus document issued and subsequently revised by the International Committee of Medical Journal Editors (ICMJE) and allegedly utilized by more than 500 journals. See International Committee of Medical Journal Editors, *Uniform Requirements for Manuscripts Submitted to Biomedical Journals*, 277 *JAMA* 927, 927 (1997).... Despite widespread utilization of the ICMJE requirements, according to a report published in the April 2001 issue of *Science and Engineering Ethics* by Sheldon Krimsky and co-authors from the University of California at Los Angeles, "[i]n reviewing 61,134 scholarly articles published in 181 academic journals in 1997, researchers ... found that just one-half of 1 percent detailed personal financial interests, including consulting arrangements, honorariums, expert witness fees, company equity and stock, and patents." Sheryl Gay Stolberg, *Scientists Often Mum About Ties To Industry*, *N. Y. Times*, Apr. 25, 2001, at A17. Moreover, those disclosures all appeared in just one-third of the 181 journals. *Id.*

Michael J. Malinowski, *Institutional Conflicts and Responsibilities in an Age of Academic-Industry Alliances*, 8 *Widener L. Symp. J.* 47, 59 n.57 (2001).

[FN182]. See Thomas, *supra* note 58, at 376.

[FN183]. The PDUFA legislation and user fee system are addressed *supra* notes 170-74 and accompanying text.

[FN184]. Commentators have estimated that there are as many as six lobbyists working in Washington, D.C. on behalf of the pharmaceutical sector for every member of Congress. Sharyl Attkisson, *Health Care Lobbyists' Rise to Power*, CBS News (Oct. 29, 2009), [http://www.cbsnews.com/stories/2009/10/20/cbsnews\\_investigates/main5403220.shtml](http://www.cbsnews.com/stories/2009/10/20/cbsnews_investigates/main5403220.shtml); see also 20/20: *Sick in America: Whose Body is it Anyway?* (ABC News television broadcast Sept. 14, 2007).

[FN185]. Angell, *supra* note 105, at 118-21; See Thomas, *supra* note 58, at 366.

[FN186]. See U.S. Food & Drug Admin., *supra* note 141, at i.

[FN187]. See *supra* note 184 and accompanying text (noting the industry's lobbying resources).

[FN188]. See *supra* note 171 for a discussion of PDUFA I-IV.

[FN189]. See Biotechnology Indus. Org., *supra* note 132, at 38; *BioBytes: The Biotech Drug Delivery Timeline*, Biotechnology Indus. Org., <http://www.bio.org/content/biobytes-biotech-drug-delivery-timeline> (last visited Dec. 29, 2011) (providing a short video discussing the drug development process); *Drug Discovery Timeline*, PhRMA, <http://www.phrma.org/media/multimedia/drug-discovery-timeline> (last visited Dec. 29, 2011) (same).

[FN190]. Consider that when former President Clinton and former Prime Minister Tony Blair made a statement on March 14, 2000, that was critical of biotechnology patenting, the sector dropped by \$100 billion over the next 24 hours. Malinowski, *supra* note 13, at 60 n.167.

[FN191]. See *supra* notes 124-125, 134 and accompanying text.

[FN192]. See generally *Genomics Revolution*, *supra* note 13 (discussing the advantages of genomics, including protein expression).

[FN193]. *Patient-Tailored Medicine Part One*, *supra* note 13, at 35 (assessing that the advent of personalized medicine is at least a decade in the future); *Patient-Tailored Medicine Part Two*, *supra* note 13, at 42.

[FN194]. Woodcock, *supra* note 135, at 93. Sophisticated genetic screening capabilities exist, but that is not the equivalent of them being commercially available. See Malinowski, *supra* note 13, at 56-58. For example, in April 2010 scientists announced a screening technique that can predict approximately three

quarters of smokers who will develop lethal lung cancers. Joseph Hall, *Smokers' Odds Just Got a Lot Better*, *Toronto Star*, Apr. 8, 2010, at A1. Science researchers also have developed a test that measures the expression of twenty-one genes to quantify the risk of breast cancer recurrence and make better treatment decisions. *Biotechnology Indus. Org.*, supra note 132, at 35. The National Institutes of Health is advancing testing in oncology through The Cancer Genome Atlas, a project to map gene variations that cause cancer, spur its growth, and cause therapeutic resistance. *Id.*

[FN195]. See *Biotechnology Indus. Org.*, supra note 132, at 2. See also supra note 141 and accompanying text. Visit the official sites of the industry's trade organizations: the Biotechnology Industry Organization ("BIO") at [www.bio.org](http://www.bio.org), and the Pharmaceutical Research and Manufacturers of America ("PhRMA") at [www.PhrMA.org](http://www.PhrMA.org).

[FN196]. See supra notes 115-20 and accompanying text (describing the rise in off-label prescribing). Protections for human subjects are afforded under the Common Rule triggered by federal funding of research and FDA regulations imposed as a condition to engage in research under its watch--to which off-label use of drugs does not apply. See 45 C.F.R. § 46.122 (2010); 21 C.F.R. § 50.1 (2010).

[FN197]. Cf. John F. Niblack, *Toward a Structured National Program to Speed the Invention and Development of New Technologies for Measuring the Progression of Chronic Diseases*, in *Biomarkers and Surrogate Endpoints: Clinical Research and Applications*, at xviii-xxi (Gregory J. Downing ed., 2000) (describing the role of genomic technology in preventing and treating chronic disease); Robert H. Glassman & Anthony Y. Sun, *Biotechnology: Identifying Advances from the Hype*, 3 *Nature Reviews: Drug Discovery* 177 (2004) (considering the causes of slow developments in biotechnology and ways to increase biotechnology value capture); David F. Horrobin, *Modern Biomedical Research: An Internally Self-Consistent Universe with Little Contact with Medical Reality?*, 2 *Nature Reviews: Drug Discovery* 151 (2003) (calling for a critical assessment of the use of in vitro and animal models to understand human disease). As observed by the FDA,

Greater success along the critical path demands greater activity in a specific type of scientific research that is directed at modernizing the product development process. Such research--highly pragmatic and targeted in its focus on issues such as standards, methods, clinical trial designs and biomarkers--is complementary to, and draws extensively from, advances in the underlying basic sciences and new technologies. Without a concerted effort to improve the critical path, it is likely that many important opportunities will be missed and frustration with the slow pace and poor yield of traditional development pathways will continue to escalate.

U.S. Food & Drug Admin., supra note 141, at 29. As stated by a proponent of applying SSRD in drug development research:

Research in biomedicine appears to rely on randomized parallel group clinical trial designs and considers these trials the "gold standard" when determining treatment effectiveness. However, large-scale trials contain inherent limitations in that they can be expensive and time consuming. In addition, patients are unique and may not respond similarly to various treatments, and in those instances a randomized

clinical trial design may be inappropriate. Guidelines are established from the averaged study findings, which may not necessarily be applicable when evaluating suitable treatment options for individuals. Specifically, patients treated in primary care settings may differ clinically from patients in the clinical trial, the patient diversity in the clinical trial may not generalize to certain patient populations, and the stringent trial criteria for accepting participants may not accurately reflect general patient populations. This is an important consideration as the field of biomedicine strives to pursue cultural competency.

Janosky et al., *supra* note 6, at 81-82 (footnotes omitted).

[FN198]. Janosky et al., *supra* note 6, at 25.

[FN199]. See *supra* Part II (addressing drug underdevelopment, including the limited number of drug targets used to treat all human ailments); *infra* Part III.C (describing the absence of regulatory oversight of drugs in light of the current dependence on the medical community on off-label drug experimentation).

[FN200]. See Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, 121 Stat. 823 (codified as amended in scattered sections of 21 U.S.C.) (authorizing fees that will go toward expediting drug development and increasing post-market drug safety); U.S. Food & Drug Admin., *supra* note 141, at 11.

[FN201]. Patient-Tailored Medicine Part One, *supra* note 13, at 28.

[FN202]. Janosky et al., *supra* note 6, at 81; see also Burke & Psaty, *supra* note 120, at 1684 (noting the individualized nature of clinical health care); Patient-Tailored Medicine Part One, *supra* note 13, at 9 (same).

[FN203]. See *supra* Part I.B.

[FN204]. Janosky et al., *supra* note 6, at 81.

[FN205]. *Id.* at 82, 95 (“Single subject designs also provide greater flexibility for treatments, as ineffective interventions can be modified over the period of study. Thus, single subject designs should be considered when conducting research in biomedicine, as the methodology and interventions can be tailored for specific individuals.” (footnotes omitted)).

[FN206]. For a thoughtful treatment of products liability in the context of pharmaceuticals, see Patient-Tailored Medicine Part Two, *supra* note 13, at 21-36.

[FN207]. See *supra* notes 78-84 and accompanying text.

[FN208]. Janosky et al., *supra* note 6, at 27-28.

[FN209]. *Id.* at 28.

[FN210]. *Id.* For further discussion of financial conflicts of interest in the research setting, see Ctr. for Health & Pharm. Law & Policy, *supra* note 81.

[FN211]. While innovative new drug returns on the HGP have been disappointing thus far, genomics has introduced a new dimension of research opportunity and is impacting clinical medicine. See Robert Goldberg & Peter Pitts, Prescription for Progress: The Critical Path to Drug Development 1, 7-9 (21st Century FDA Task Force Working Paper, 2006), available at [http://www.manhattan-institute.org/pdf/CMP\\_FDA\\_Task\\_Force.pdf](http://www.manhattan-institute.org/pdf/CMP_FDA_Task_Force.pdf); Patient-Tailored Medicine Part One, *supra* note 13, at 8-9.

[FN212]. See Patient-Tailored Medicine Part One, *supra* note 13, at 7, 16-17.

[FN213]. Personalized Med. Coal., The Case for Personalized Medicine 4 (2006), available at <http://www.cspo.org/outreach/md/docs/TheCaseforPersonalizedMedicine.pdf>; Patient-Tailored Medicine Part One, *supra* note 13, at 16-17.

[FN214]. Lyle J. Palmer et al., Pharmacogenetics of Asthma, 165 *Am. J. Respiratory & Critical Care Med.* 861, 861 (2002); Alix Weisfeld, Comment, How Much Intellectual Property Protection Do the Newest (and Coolest) Biotechnologies Get Internationally?, 6 *Chi. J. Int'l L.* 833, 835 (2006).

[FN215]. See *supra* notes 160, 168, and 200 and accompanying text.

[FN216]. Professor Janosky provides a full annotated bibliography of SSRD articles recently published in PsycInfo, MEDLINE, and PubMed. Janosky et al., *supra* note 6, at 97-114.

[FN217]. See *supra* note 7 and accompanying text.

[FN218]. Janosky et al., *supra* note 6, at 83.

[FN219]. *Id.* at 82-84.

[FN220]. *Id.* at 82 (footnotes omitted).

[FN221]. *Id.* at 1.

[FN222]. Green, *supra* note 6, at 79.

[FN223]. Inst. of Med., *Small Clinical Trials: Issues and Challenges* 57-59 (Charles H. Evans, Jr. & Suzanne T. Ildstad eds., 2001).

[FN224]. *Id.* at 16 tbl.1-2; see also Janosky et al., *supra* note 6, at 2 (discussing the IOM Report and elaborating on SSRD methodology).

[FN225]. See *supra* notes 78-79 and accompanying text.

[FN226]. Over the last five years, Phase III trials have expanded from 3000 to 20,000 subjects and their cost has doubled to reach \$100 million. See *supra* note 79 and accompanying text.

[FN227]. Inst. of Med., *A National Cancer Clinical Trials System for the 21st Century* 29 (2010); Opinion, *Faltering Cancer Trials*, N.Y. Times, Apr. 25, 2010, at A11.

[FN228]. Johnston & Pennypacker, *Strategies and Tactics*, *supra* note 7, at 304. Johnston and Pennypacker propose that researchers “not create group data until they have already conducted a thorough analysis of the individual data that is included.” *Id.*

[FN229]. *Id.* As explained by Johnston and Pennypacker, “One reason for this rule is that group data obscures individual patterns of responding. Regardless of whether the collated data present an interesting or expected picture, they do not necessarily represent what can be seen by looking at the records from each individual subject.” *Id.*

[FN230]. *Id.* at 298.

[FN231]. Imposing SSRD as a substitute for GD is not practicable or even desirable at this time. See *supra* notes 189-90 and accompanying text.

[FN232]. See *supra* Part I.A (discussing the phases of the clinical trial process).

[FN233]. See *supra* notes 228-30 and accompanying text.

[FN234]. See Inst. of Med., *supra* note 227, at 99 (describing a new strategy of using small “targeted trial designs”); Janosky et al., *supra* note 6, at 93-95 (describing the use of SSRD for a patient study involving a forty-two-year-old mixed race male with elevated blood pressure). “Treatments are often unavailable for unique patient populations or rare disorders, and researchers are left uncertain what designs or tools to use when implementing treatments.” *Id.* at 82.

[FN235]. Janosky et al., *supra* note 6, at 28-29 (footnotes omitted).

[FN236]. See *id.* at 82. “This methodology is also particularly suited for primary care practice-based research, where practitioners can tailor individualized treatments to improve outcomes.” *Id.* at 29.

Tsapas and Matthews discussed that N-of-1 trials can be an optimal approach when treating chronic diseases such as diabetes mellitus, which frequently rely on clinical judgment and arbitrary criteria. The authors stated that guidelines for treating diabetes have been criticized as being unreliable, as algorithms are generally established from “clinical judgment and experience.” Single subject designs take into account the uniqueness of the individual, rather than using a standardized treatment that may not be effective for all diabetics.

Id. at 83 (footnote omitted).

[FN237]. Id. at 95. For documentation of the use of SSRD in biomedicine, see Janosky et al., *supra* note 6, at 97-114.

[FN238]. Patient-Tailored Medicine Part One, *supra* note 13, at 5.

[FN239]. See *supra* Part II.B.

[FN240]. Press Release, U.S. Food & Drug Admin., FDA Works to Speed the Advent of New, More Effective Personalized Medicine (Mar. 22, 2005), available at <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2005/ucm108423.htm>. As stated by the FDA,

This guidance is intended to facilitate scientific progress in the field of pharmacogenomics and to facilitate the use of pharmacogenomic data in drug development. The guidance provides recommendations to sponsors holding investigational new drug applications (INDs), new drug applications (NDAs), and biologics license applications (BLAs) on (1) when to submit pharmacogenomic data to the Agency during the drug or biological drug product development and review processes, (2) what format and content to provide for submissions, and (3) how and when the data will be used in regulatory decision making.

U.S. Food & Drug Admin., Guidance for Industry: Pharmacogenomic Data Submissions 1 (2005), available at <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126957.pdf> (footnote omitted) [hereinafter U.S. Food & Drug Admin., Guidance]. For discussion of the clinical applications of pharmacogenomics and use of it to tailor therapies, see Pharmacogenomics and Its Role in Drug Safety, FDA Drug Safety Newsl. (U.S. Food & Drug Admin, Wash., D.C.), Winter 2008, at 24, available at <http://www.fda.gov/downloads/Drugs/DrugSafety/DrugSafetyNewsletter/ucm109169.pdf>. The FDA and the European Medicines Agency (“EMA”) have promoted the voluntary submission of genomic data jointly. U.S. Food & Drug Admin. & Eur. Meds. Agency, Guiding Principles: Processing Joint FDA EMA Voluntary Genomic Data Submissions within the framework of the Confidentiality Arrangement (2006), available at <http://www.fda.gov/downloads/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm085378.pdf>; Federico Goodsaid, U.S. Food & Drug Admin., Joint USFDA-EU Pharmacogenomic Initiatives (2006), available at <http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ucm119097.pdf>



(presentation on joint FDA-EU pharmacogenomic initiatives). To implement the guidelines and develop related policy and standards, the FDA created the Interdisciplinary Pharmacogenomic Review Group (“IPRG”). See Ctr. for Drug Evaluation and Research, U.S. Food & Drug Admin., Manual of Policies and Procedures 4180.2: Management of the Interdisciplinary Pharmacogenomics Review Group (IPRG) (2005), available at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/StaffPoliciesandProcedures/ucm073574.pdf> (setting out the charter for and duties of the IPRG). The FDA also has issued a decision tree for genomic data submission. U.S. Food & Drug Admin., Guidance, *supra*, at 19.

[FN241]. Woodcock, *supra* note 135, at 93.

[FN242]. Although 121 new drug labels contain pharmacogenomic information with sixty-nine of them referring to human genomic biomarkers, more than sixty-two percent of those with human genomic information contain information related to drug metabolism and a large portion of the rest is associated with cancer treatments. Felix W. Frueh et al., Pharmacogenomic Biomarker Information in Drug Labels Approved by the United States Food and Drug Administration: Prevalence of Related Drug Use, 28 *Pharmacotherapy* 992, 994-95 (2008). A noted example is the association between over expression of the genetic variance Her-2/neu and the breast cancer drug Herceptin. See generally Bazell, *supra* note 138 (describing this association in depth). Experience to date suggests that drug sponsors' fear that pharmacogenomics data in the regulatory process will splinter their markets is not fully grounded given physician discretion and inclination to use drugs off label, including in combination with other drugs. For example, though Herceptin was developed to treat a very specific form of aggressive breast cancer associated with over expression of the protein HER2, physicians have used it off label to treat others with some success. In fact, in combination with Taxol, Herceptin has even been discovered to treat prostate cancer. Herceptin and Taxol Combination Looks Promising for Prostate Cancer, *PSA Rising Mag.*(Nov. 3, 1999), <http://www.psa-rising.com/medicalpike/herceptintaxol.htm>.

[FN243]. Kelly C. Lee et al., *Pharmacogenomics: Bridging the Gap Between Science and Practice*, 50 *J. Am. Pharm. Assoc.* e1, e2 (2010).

[FN244]. See, e.g., *Ass'n of Am. Physicians and Surgeons, Inc. v. FDA*, 226 F. Supp. 2d 204, 217-18 (D.D.C. 2002); *infra* notes 248-61 and accompanying text (challenging FDA rules proposing mandatory pediatric trials).

[FN245]. H.R. Rep. No. 105-310, at 60 (1997).

[FN246]. See *Wash. Legal Found. v. Henney*, 202 F.3d 331, 336-37 (D.C. Cir. 2000). At issue in the case were “the FDA's and Congress' attempts to regulate two ... promotional strategies: manufacturer dissemination to physicians of independent medical and scientific publications concerning the off-label uses of their products” (referred to as “enduring materials”), “and manufacturer support for Continuing Medical Education (CME) programs for doctors that focus on off-label uses.” *Id.* at 332-33.

[FN247]. *Id.* at 336.

[FN248]. While it is a common practice for physicians to prescribe to children pharmaceuticals only approved for adult use, by doing so, they can expose children to various hazards. Children may be given an ineffective dose or an overdose, and they face an increased risk of side effects. Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, 62 Fed. Reg. 43,900, 43,901 (Aug. 15, 1997) (codified at 21 C.F.R. pts. 201, 312, 314, 601). This happens because:

Correct pediatric dosing cannot necessarily be extrapolated from adult dosing information using an equivalence based either on weight ... or body surface area .... Potentially significant differences in pharmacokinetics may alter a drug's effect in pediatric patients. The effects of growth and maturation of various organs, maturation of the immune system, alterations in metabolism throughout infancy and childhood, changes in body proportions, and other developmental changes may result in significant differences in the doses needed by pediatric patients and adults.

*Id.* Faced with insufficient information about a new medication, pediatricians often opt to prescribe their young patients older, less effective, but well-tested medication--as opposed to newer, more effective medication that has not been subjected to rigorous study on pediatric populations. *Id.* at 43,900. This practice keeps children from benefitting from state-of-the-art medication. See Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, 63 Fed. Reg. 66,632, 66,632 (Dec. 2, 1998) (codified at 21 C.F.R. pts. 201, 312, 314, 601). Ironically, the status of children as a “protected group” under federal regulations to protect human subjects contributes to their exclusion as a study focus in clinical research. See 45 C.F.R. §§ 46.401-409 (2010) (setting out the restrictions on research involving children).

[FN249]. See *supra* note 21-22 and accompanying text; Carolina Martinez-Castaldi et al., *Child Versus Adult Research: The Gap in High Quality Study Design*, 122 *Pediatrics* 52, 52 (2008).

[FN250]. U.S. Food & Drug Admin., *The Pediatric Exclusivity Provision: January 2001 Status Report to Congress*, at iii (2001).

[FN251]. See *Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Revision of “Pediatric Use” Subsection in the Labeling*, 59 Fed. Reg. 64,240 (Dec. 13, 1994) (codified at 21 C.F.R. pt. 201).

[FN252]. *Ass'n of Am. Physicians and Surgeons, Inc. v. FDA*, 226 F. Supp. 2d 204, 218 (D.D.C. 2002) (quoting David Kessler, FDA Comm'r, *Address to the American Academy of Pediatrics* (Oct. 14, 1992)).

[FN253]. *Food and Drug Administration Modernization Act of 1997*, Pub. L. No. 105-115, § 111, 111 Stat. 2296, 2305-09 (codified at 21 U.S.C. § 355a (2006)).

[FN254]. *Id.*; 21 U.S.C. § 355a(b)-(c) (2006). The FDA interpreted the provision broadly and provided the six-month extension to all drugs derived from the active moiety put under pediatric study. U.S. Food & Drug Admin., *supra* note 250, at 7.

[FN255]. Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, 63 Fed. Reg. 66,632 (Dec. 2, 1998) (codified at 21 C.F.R. pts. 201, 312, 314, 601).

[FN256]. 5 U.S.C. §§ 701-706 (2006).

[FN257]. Ass'n of Am. Physicians and Surgeons, 226 F. Supp. 2d at 222.

[FN258]. U.S. Gov't Accountability Office, GAO-01-705T, *Pediatric Drug Research: Substantial Increase in Studies of Drugs for Children, But Some Challenges Remain* 4 (2001). By September 30, 2002, the FDA had issued a total of 256 written requests. Michelle Meadows, *Drug Research and Children*, FDA Consumer, Jan.-Feb. 2003, at 12, 15. For information about the Act, visit the official Internet site at Best Pharmaceuticals for Children Act, Nat'l Insts. Health, <http://bpca.nichd.nih.gov/> (last modified Dec. 13, 2011).

[FN259]. U.S. Gov't Accountability Office, *supra* note 258, at 2.

[FN260]. William Rodriguez et al., *Adverse Drug Events in Children: The U.S. Food and Drug Administration Perspective*, 62 *Current Therapeutic Res.* 711, 718 (2001).

[FN261]. S. Rep. No. 107-79, at 1-2 (2001).

[FN262]. 21 U.S.C. § 355a(j) (2000).

[FN263]. Best Pharmaceuticals for Children Act, Pub. L. No. 107-109, 115 Stat. 1408 (2002) (codified as amended in scattered sections of 21 U.S.C. and 42 U.S.C.); see H.R. Rep. No. 107-277, at 14 (2001) (explaining that while the incentive had been successful, it was not adequate to address the need for studies in certain drugs such as those with no patent protection or those for neonates); S. Rep. No. 107-79, at 2 (2001) (noting the success of the 1997 legislation as well as the need to augment its provisions).

[FN264]. See 42 U.S.C. § 284m(a), (b) (2006).

[FN265]. In the words of the court, "After examining: (1) specific provisions of the FDCA, as well as the Act's broader context; (2) the legislative history of the BPCA; and (3) the conflict between the BPCA and Pediatric Rule, this court concludes that Congress has directly spoken to the issue here and has precluded the FDA's jurisdiction to promulgate the Pediatric Rule." *Ass'n of Am. Physicians and Surgeons, Inc. v. FDA*, 226 F. Supp. 2d 204, 212 (D.D.C. 2002).

[FN266]. Lauren Hammer Breslow, Note, The Best Pharmaceuticals for Children Act of 2002: The Rise of the Voluntary Incentive Structure and Congressional Refusal to Require Pediatric Testing, 40 Harv. J. on Legis. 133, 134 (2003). For example, BPCA is costly:

While the BPCA is a strong step forward for children's health, it comes at a significant price. The six-month patent extensions cost consumers hundreds of millions of dollars because of the delay in cheaper, generic drugs reaching the market. In addition to the patent extensions, taxpayers will fund the drug studies that manufacturers refuse to conduct, which average about \$3.87 million per drug. For fiscal year 2002, Congress appropriated \$200 million to that end.

Id. (citing Pub. Citizen Congress Watch, *Patently Offensive: Congress Set to Extend Monopoly Patents for Cipro and Other Drugs 2* (2001), available at <http://www.citizen.org/documents/ACF34F.pdf>).

[FN267]. 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).

[FN268]. "As of Feb. 19, 2008, 145 drugs have been granted pediatric exclusivity." Id. at 548 n.160.

[FN269]. Orphan Drug Act, Pub. L. No. 97-414, §§ 2, 4, 96 Stat. 2049, 2050-51, 2053-56 (1983) (codified as amended at 21 U.S.C. § 360cc; 26 U.S.C. 45C (2006)); Mark D. Shtilerman, *Pharmaceutical Inventions: A Proposal for Risk-Sensitive Rewards*, 46 IDEA 337, 342-43 (2006).

[FN270]. Orphan Drug Designation (ODD) Information, Clinuvel, <http://www.clinuvel.com/pharmaceutical-regulation/orphan-drugs> (last visited Dec. 29, 2011).

[FN271]. See *supra* Part III.B.

[FN272]. See *supra* note 220-22 and accompanying text.

[FN273]. See U.S. Gov't Accountability Office, *supra* note 67, at 18; Inst. of Med., *supra* note 67, at 1.

[FN274]. See *supra* note 265.

[FN275]. Harris, *supra* note 2.

[FN276]. Id.

[FN277]. See Aldes, *supra* note 54, at 464 ("Part of this oversight involves accounting for changes in medicine and trial design both of which affect drug testing. As such, the FDA must acknowledge when changes occur, and subsequently modify protocols and regulations that govern the affected clinical trials." (footnote omitted)).

[FN278]. Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, 121 Stat. 823 (codified as amended in scattered sections of 21 U.S.C.); see supra notes 23-25, 67 and accompanying text; supra Part II.

[FN279]. See supra Part II.B.

[FN280]. See supra Parts III.A-B.

[FN281]. Janosky et al., supra note 6, at 95.

[FN282]. See supra notes 35-36 and accompanying text.

[FN283]. See Harris, supra note 2.

[FN284]. Id.

[FN285]. See supra Part II.

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