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Realizing the Potential for Biomarkers in Imaging: Background and Legal Basis

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I. INTRODUCTION

Advances in the pharmaceutical and medical device industries have contributed substantially to the health of the American people as well as the global population, with continued research holding the promise of even greater improvements in the future. The high and increasing cost of product development, however, in terms of time and resources necessary to gain Food and Drug Administration (FDA) marketing approval, threatens to seriously impact the pace of innovation. The appropriate use of medical imaging, in both the preclinical and clinical settings, offers the prospect of more efficient medical product evaluation, cutting development timeframes and reducing cost.

Crucial to imaging's emerging role in medical product development is the concept of biomarkers. This generic term applies to all detection methods used in the life sciences and may be defined as any detectable biological parameter whether biochemical, genetic, histological, anatomic, physical, functional, or metabolic. By logical extension, imaging biomarkers are any anatomic, physiologic, biochemical, or molecular parameter detectable by one or more imaging methods used to establish the presence and/or severity of disease.

Clinical scientists and industry researchers have recognized biomarkers, including imaging biomarkers, as suitable endpoints for clinical trials. More importantly, statutes and regulations support the use of imaging biomarkers as surrogate endpoints in the preclinical and clinical evaluation of drugs and medical devices. This article overviews this legal basis and suggests a paradigm for appropriate application of imaging biomarkers. In order to fully understand that basis, it is first necessary to review the Food and Drug Administration's (FDA's) paradigm for approving new drugs and medical devices.

II. FDA APPROVAL OR CLEARANCE FOR DRUGS AND MEDICAL DEVICES

The Federal Food, Drug and Cosmetic Act (FDCA), enacted in 1938 and administered by FDA, establishes an elaborate set of regulatory controls governing the marketing of medical products.[1] These regulations, modified and amended over the years, require that new drugs and devices be safe and effective for their intended use(s) before they

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[1] Federal Food, Drug, and Cosmetic Act, Pub. L. No. 75-717, 52 Stat. 1040 (1938) (codified as amended at 21 U.S.C. §§ 301-397 (2004)).

may be distributed in the market.[2] Establishing this safety and efficacy for genuinely new medical products generally requires preclinical and clinical trials, a process that takes many years and millions of dollars per product.[3]

A. *The Drug Approval Process*

Pursuant to the FDCA, as amended by the 1962 Drug Amendments[4] and the 1997 Food and Drug Administration Modernization Act (FDAMA),[5] FDA approval is required before new drugs can be marketed legally in the United States.[6] To gain FDA approval, sponsors of new drugs must provide the agency with "substantial evidence" of safety and effectiveness, a process that requires submission of an investigational new drug (IND) application,[7] agency approval of the IND and clinical trial protocol, as well as approval from the local institutional review board (IRB) at the facilities where the proposed studies will take place. FDA generally requires completion of three phases of human clinical trials to establish safety and efficacy of new drugs, each one progressively expansive in scope, duration, and cost.[8] Within this context, agency regulations ordinarily require at least two adequate and well-controlled studies to prove safety and efficacy.[9] Following completion of the human clinical trials and approval of the new drug application (NDA), a document that includes a full report of all of the study results, the drug may be marketed.[10] In some instances, FDA may require further studies following drug approval, known as postmarket studies, to collect additional safety and effectiveness data.[11]

B. *Medical Device Approval Process*

Under the FDCA, as modified by the 1962 Drug Amendments, the 1976 Medical Device Amendments (MDA),[12] and FDAMA, among others,[13] medical devices also must be shown to be safe and effective to gain FDA approval. Paralleling the new drug system, new devices cannot be marketed legally in the United States without first receiving agency approval. The device approval/clearance paradigm differs from the new drug model, however, in two important respects: 1) a three-tiered risk-based system is used to categorize devices according to perceived risk to patients; and 2) marketing approval is based on a sequential process that can vary depending on the class of device and its overall risk.

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[2] *See id.* at § 903, 21 U.S.C. § 393 (1995 & Supp. III 1998).

[3] *See* PETER TOLLMAN ET AL., A REVOLUTION IN R&D: HOW GENOMICS AND GENETICS ARE TRANSFORMING THE BIOPHARMACEUTICAL INDUSTRY (Boston Consulting Group 2001), *available at* http://www.bcg.com/publications/files/eng_genomicsgenetics_rep_11_01.pdf (last visited Nov. 18, 2005) [hereinafter BCG REPORT]; *see* Michael D. Greenberg, *Aids, Experimental Drug Approval, and the FDA New Drug Screening Process*, 3 NYU J. LEGIS. & PUB. POL'Y 295, 306 (2000).

[4] Drug Amendments of 1962, Pub. L. No. 87-781, 76 Stat. 780 (codified as amended in scattered sections of 21 U.S.C.).

[5] Food and Drug Administration Modernization Act, Pub. L. No. 105-115, 111 Stat. 2295 (1997).

[6] *See generally* Greenberg, *supra* note 3.

[7] *See* 48 Fed. Reg. 26,720, 26,723 (1983) (codified as amended at 21 C.F.R. § 312.23(a) (1999)).

[8] *See* 21 C.F.R. § 312.21; *see generally* Greenberg, *supra* note 3, at 302-08.

[9] *See* 28 Fed. Reg. 6378 (1963).

[10] *See* 21 C.F.R. § 314.50 (1999).

[11] *See id.* § 312.85.

[12] Medical Device Amendments of 1976, Pub. L. No. 94-295, 90 Stat. 539 (1976) (codified as amended in scattered sections of 21 U.S.C.).

[13] Safe Medical Devices Act of 1990, Pub. L. No. 101-629, 104 Stat. 4511 (codified in scattered sections of 21 U.S.C. and 42 U.S.C. § 263); Medical Device Amendments of 1992, Pub. L. No. 102-3000, 106 Stat. 238 (codified in scattered sections of 21 U.S.C. and 42 U.S.C. § 262).

The MDA placed existing devices into one of three classes according to the degree of risk posed by the device.[14] Class I and II include low and moderate risk devices, respectively, with class II products subject to special controls above and beyond the general controls applicable to all classes of devices. Class III products are those products that support or sustain human life, prevent impairment of human health, or pose an unreasonable risk to patient safety.[15] These products are regulated individually, with manufacturers required to establish safety and effectiveness to secure marketing approval. This risk-based three-tiered system is applicable retroactively to devices marketed prior to 1976, as well as to products introduced after implementation of the MDA.

The marketing approval process for devices introduced after 1976 varies, depending on perceived patient risk and whether there are similar, existing legally-marketed products. Initially, certain low-risk devices are exempted from the section 510(k) premarket notification requirement under FDAMA provisions intended to focus agency resources on higher risk devices.[16] Devices not 510(k) exempt are subject to premarket notification provisions, which require manufacturers to notify the agency of their intention to market a new product and provide the agency with a detailed description of that device.[17] From this data, which generally is nonclinical, FDA determines whether the new device is "substantially equivalent" to an existing, legally-marketed product known as a "predicate" device.[18] Should the agency determine that the new device is substantially equivalent, that new product is "cleared" for market and generally is subject to regulations applicable to the predicate device.

Genuinely new post-1976 devices that are not "substantially equivalent" to a predicate product are placed into class III and are subject to the premarket approval (PMA) process, although there are provisions to down-classify new products into class I or class II if their patient risk profiles warrant inclusion in these classes.[19] Class III devices subject to the PMA process must establish reasonable safety and effectiveness prior to marketing, an exercise much more demanding than the 510(k)/substantial equivalence pathway and similar to the NDA process, as multiple phases of preclinical and clinical trials often are required.[20]

III. ESTABLISHING SAFETY AND EFFECTIVENESS: THE PROSPECTIVE, RANDOMIZED, WELL-CONTROLLED STUDY

Under FDA's regulatory regime, proof of safety and efficacy of new medical products requires valid data from scientific studies. The agency recognizes that the quality of scientific data can differ depending on the experimental design of a preclinical or clinical trial. FDA's preferred clinical trial design is the prospective, randomized, well-controlled, double-blind study, which is considered the reference or "gold standard." Such trials typically employ traditional trial endpoints such as morbidity and mortality to evaluate

[14] *See* MDA § 513(a), Pub. L. No. 94-295, § 513(a), 90 Stat. 539, 540-41 (1976) (codified as amended at 21 U.S.C. § 360c(a) (1994)).

[15] *See id.*

[16] *See* FDAMA, Pub. L. No. 105-115, 111 Stat. 2295 (1997).

[17] *See* Medical Device Amendments of 1976, Pub. L. No. 94-295, 90 Stat. 539 (1976) (codified as amended in scattered sections of 21 U.S.C.); *see generally* Richard A. Merrill, *The Architecture of Government Regulation of Medical Products*, 82 VA. L. REV. 1753 (1996).

[18] MDA, Pub. L. No. 94-295, § 510(k), 90 Stat. 539, 580 (1976) (codified as amended at 21 U.S.C. §360(k) (1994)).

[19] *See* Merrill, *supra* note 17, at 1809.

[20] *See id.* at 1821.

outcome. Despite this preference, the agency does not always require its use, particularly in the evaluation of medical devices.

Establishing new drug safety and effectiveness generally requires sponsors to complete three phases of human clinical trials, and in some cases, a fourth phase of postmarketing studies. Pursuant to the FDCA, FDA cannot grant marketing approval when research data show that a drug is unsafe, or when there is a "lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed."[21] Substantial evidence is defined as, "evidence consisting of adequate and well-controlled investigations," including clinical investigations by qualified experts.[22] Based on implicit references in Congress's use of the plural "investigations" found in the 1962 Drug Amendments to section 505(b), as well as the long-established scientific paradigm that results are not reliable unless replicated, FDA generally requires two adequate, well-controlled Phase III studies demonstrating effectiveness of a drug to gain marketing approval, although exceptions have been made.[23] In fact, shortly after passage of the 1962 Drug Amendments, FDA promulgated regulations supporting the requirement of two investigations as "ordinarily" necessary to gain agency approval.[24] The agency has never formalized this requirement for all instances of new drug marketing approvals, however, preferring instead to retain some level of discretion in deciding how many investigations to require on a case-by-case basis.[25]

While FDA's scientific evidence standards and pathway for proof of new drug safety and effectiveness are rigid, the analogous process for medical devices can be less demanding, as evidenced by applicable provisions of the FDCA as well as the agency's explicit hierarchy of valid scientific evidence for medical devices.[26] Unique to the medical device regulatory regime is product classification based on perceived risk to patients. Sponsors of class I, class II, and pre-1976 class III devices for which FDA has not requested proof of safety and effectiveness need only establish "substantial equivalence" to legally market their new products, a process that does not ordinarily require clinical trials.[27] For devices without predicates that must undergo PMA, the approval process is substantially similar to the rigorous requirements for new drugs, although there are important differences. First, sponsors of PMA devices are required to provide the agency with "reasonable assurance" of safety and effectiveness.[28] No such qualifying language is found in the parallel drug provisions. In addition, the device provisions allow for the Secretary of the Department of Health and Human Services (HHS) to make a determination of effectiveness based on scientific evidence other than well-controlled investigations, a standard also absent from the drug provisions.[29] Furthermore, the legislative history of the medical device provisions of the MDA illustrates the intent of Congress to allow for a more flexible standard than that applicable to drugs.[30]

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[21] 21 U.S.C. § 355(d)(2), (d)(5) (1988).

[22] Application for FDA Approval to Market a New Drug, 21 C.F.R. § 314.50(f)(1) (2001).

[23] *See* FDCA § 505(b) (requiring "full reports of investigations" for agency approval); *see* 21 C.F.R § 314.126(b)(2)(i) (1995); *see generally* Merrill, *supra* note 17, at 1849.

[24] *See* Proposed Rule Making: New Drugs, 28 Fed. Reg. 1448, 1450 (Feb. 14, 1963); *see* Rules and Regulations: New Drugs, 28 Fed. Reg. 6377, 6378 (June 20, 1963).

[25] *See* Rules and Regulations: New Drugs, 39 Fed. Reg. 9750, 9755 (Mar. 13, 1974).

[26] 21 C.F.R. § 860.7 (1988).

[27] *See* Pub. L. No. 94-295, § 510(k), 90 Stat. 539 (1976) (codified as amended at 21 U.S.C. §360(k) (1994)).

[28] *See* FDCA § 513(a), 21 U.S.C. § 360c.

[29] *See* FDCA § 513(a)(2)-(3), 21 U.S.C. § 360c(a)(2)-(3) (1994).

[30] *See* Peter Barton Hutt, Richard A. Merrill & Alan M. Kirschenbaum, *The Standard of Evidence Required for Premarket Approval Under the Medical Device Amendments of 1976*, 47 FOOD & DRUG L.J. 605 (1992).

FDA has promulgated regulations explicitly outlining the types of evidence necessary for establishing device safety and effectiveness. In this hierarchy of valid scientific evidence, the prospective, randomized, well-controlled, double-blind study design is the preferred trial design for establishing safety and efficacy.[31] The agency explicitly accepts other study designs, however, because the gold standard design is not always possible or practical when applied to medical devices. Specifically, partially-controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human clinical experience with a marketed product as evidence of safety and effectiveness are specifically enumerated, in that order.[32] Explicitly excluded from the agency's definition of valid scientific evidence are isolated case reports, random experience, reports lacking sufficient detail to permit scientific evaluation, and unsubstantiated opinions.[33]

IV. LIMITATIONS POSED BY THE PROSPECTIVE, RANDOMIZED, WELL-CONTROLLED STUDY

Prospective, randomized, well-controlled, double-blind studies are not without their limitations. Various technical, ethical, and cost factors pose potentially significant issues to their effective and efficient application in a variety of settings.

A. *Technical Issues*

Application of the prospective, randomized, well-controlled, double-blind study design to any clinical trial poses considerable technical challenges. Recruitment of patients in numbers sufficient to achieve statistical significance often is difficult, time consuming, and, in some cases, impossible. Initially, for diseases with very low prevalence, identifying and successfully enrolling patients may be a major undertaking.[34] Second, patients may be unwilling to enter a randomized clinical trial and risk not receiving the treatment under investigation, which often is perceived by the lay public as superior to existing therapies. Finally, where patients aggressively seek and use existing traditional and nontraditional treatments, recruitment for clinical trials may be difficult, as patients are unwilling to risk foregoing their current therapies. For example, patient recruitment for clinical trials of early AIDS medications proved difficult because patients were disinclined to give up their current therapies in favor of the unproven therapies that were being studied in the clinical trials.[35]

B. *Ethical Challenges*

Ethical challenges posed by the prospective, randomized, well-controlled, double-blind study design also are a limiting factor, impacting the use of a placebo control group. For example, it is unethical to withhold a clinically-accepted treatment from those patients randomized to a control group, making comparison of the treatment group to a traditional placebo group impossible. Similarly, where a sponsor seeks an additional indication for a product that already has been used extensively off-label and has become the standard of

[31] 21 C.F.R. § 860.7.

[32] *See id.*

[33] *See id.*

[34] R.J. Lilford, J.G. Thornton & D. Braunholtz, *Clinical Trials and Rare Diseases: A Way Out of a Conundrum*, 311 BRIT. MED. J. 1621 (1995).

[35] *See* Greenberg, *supra* note 3, at 317.

care, comparison to a traditional control group becomes difficult. This has been seen with orthopedic pedicle screws for posterior spinal fixation, where years of off-label use made the product the medical standard of care for a number of conditions, thus making designing a trial to validate those off-label indications problematic.[36]

C. *Cost and Timeframe Issues*

The long timeframes and substantial costs associated with clinical trials is another major issue that figures prominently in a company's decision to pursue a given trial. On average, it takes over a decade and hundreds of millions of dollars to bring a new pharmaceutical from early research and development to final FDA marketing approval, with lower but still substantial figures for genuinely new medical devices.[37] As a result of these significant costs, sponsors must make practical financial decisions with respect to the types of medical products in which they invest. Often, this means focusing on common diseases with large patient populations—markets with the best potential to recoup substantial development costs.[38]

In addition to impacting which new medical products are brought to market, the high costs associated with clinical trials also affect who brings these products to market. While these substantial costs may be borne by large pharmaceutical concerns or major medical device manufacturers, smaller companies usually lack the resources to independently undertake new medical product development. This often forces such firms to choose between licensing their product to larger entities or forgoing development altogether.

Most importantly, long timeframes and high costs that may impede product development have a real impact on patients in need. Simply put, any unnecessary delay in bringing a safe and effective therapy to market means patients who would have benefited from that product must do without. While this is difficult to quantify, there is little question that long product evaluation timeframes have the potential to increase patient morbidity and mortality.

D. *Reliance on Traditional Endpoints*

Apart from the technical, ethical, and cost issues associated with the current clinical research standards, the prospective, randomized, well-controlled, double-blind design has inherent limitations. Such trials rely on traditional endpoints to determine whether a new drug or device is safe and effective. These benchmarks, or "true" endpoints, focus on mortality and morbidity, serving as comparison points in determining whether new drugs or devices decrease the rate of death in the case of mortality, or increase the functionality or quality of life of patients in the case of morbidity.

Traditional endpoints can pose considerable practical difficulties in the clinical trial setting. Mortality measures require significant time for patient follow-up and are susceptible to complicating factors (e.g., loss to follow-up and intercurrent illness). For example, many cancer therapies evaluate survival at significant time intervals, typically years following cessation of therapy. Such timeframes make it difficult and expensive to track patients, and increase the risk that patients may die from conditions that may or may not be related to the therapy in question.

[36] Orthopedic Devices: Classification, Reclassification, and Codification of Pedicle Screw Spinal Systems, 60 Fed. Reg. 51,946-57 (1995) (proposed Oct. 4, 1995).

[37] *See* BCG REPORT, *supra* note 3.

[38] *See* Merrill, *supra* note 17, at 1790 (discussing the Orphan Drug Amendments).

The measure of morbidity, although it may involve shorter timeframes than mortality, is subjective by nature, resulting in potentially less definitive results. Pain, for instance, is used as a morbidity endpoint in clinical trials examining analgesic medications, with the presence and severity of pain reported by the patients themselves. While it is possible to confirm that a patient personally completed such reports, it is impossible to objectively verify pain data using traditional methods.

V. BIOMARKERS IN IMAGING AS SURROGATE ENDPOINTS: ADDRESSING EXISTING LIMITATIONS OF CURRENT CLINICAL TRIAL STANDARDS

Addressing the technical, ethical, cost, and inherent limitations posed by the prospective, randomized, placebo-controlled, double-blind trial design relied on by scientists, researchers, and FDA, while maintaining FDA's high standards for establishing safety and effectiveness, is and will continue to be a challenge. The appropriate application of surrogate endpoints, including imaging biomarkers, is one approach to successfully meeting this challenge.

A surrogate endpoint, also referred to as a "marker," is a "laboratory measurement or physical sign that is used in therapeutic trials as a substitute for a clinically meaningful endpoint that is a direct measure of how a patient feels, functions, or survives and that is expected to predict the effect of the therapy."[39] The more specific term "biomarker" applies to all detectable biological parameters including biochemical, genetic, histological, anatomic, physical, functional, or metabolic.[40] By logical extension, imaging biomarkers are defined as any anatomic, physiologic, biochemical, or molecular parameter detectable by imaging methods, and used to establish the presence and/or severity of disease.[41]

Key to the tremendous potential of biomarkers in imaging is that many medical therapies alter parameters that may be quantified by such biomarkers, potentially allowing their broad application to the evaluation of new medical therapies. Furthermore, a well-developed medical imaging infrastructure already exists, with a vast array of equipment already in place in hospitals, clinics, and research laboratories. Radiologists, cardiologists, and other imaging professionals use biomarkers in imaging every day to gauge the effectiveness of medical treatments, ranging from the simple measurements of tumor mass to more complex MRI sequences. Together with this infrastructure, the appropriate use of biomarkers in imaging may allow less extensive and costly preclinical and clinical trials, thereby improving the efficiency of medical product development and enhancing the timely clinical introduction of new therapies.

In the preclinical environment, biomarkers in imaging may allow early safety and proof-of-concept determinations, and perhaps reduce the number of animals necessary to successfully complete preclinical studies. For example, use of a new compound, modified with a radioactive substance that can be traced and quantified, can define its pharmacokinetics and pharmacodynamics. Perhaps more importantly, imaging biomarker use in the preclinical setting may allow researchers to identify promising new therapies more quickly, as well as convincingly demonstrate that other products hold no such promise, thus greatly improving the efficient evaluation of the vast number of drugs and devices in the initial stages of evaluation.

The potential of biomarkers in imaging as surrogate endpoints also can be seen in the unique characteristics of imaging modalities. Such imaging often allows for the identifi-

[39] *See* 57 Fed. Reg. 132,234 (Apr. 15, 1992).

[40] *See* John J. Smith et al., *Biomarkers in Imaging: Realizing Radiology's Future*, 227 RADIOLOGY 633-38 (2003).

[41] *See id.*

cation of incremental changes in disease conditions, changes typically missed with traditional evaluation approaches. Computerized tomography (CT) scanning, for example, can detect small changes in the size of a liver tumor, changes impossible to gauge from a physical examination. Similarly, positron emissions tomography (PET) can demonstrate subtle changes in tumor metabolism.

Notwithstanding the unique contributions of imaging biomarkers as surrogate endpoints in the research setting, these biomarkers also address many inherent limitations associated with traditional endpoints in both preclinical and clinical trials. Appropriate application of biomarkers in imaging allows for compressed evaluation timeframes as compared to long-lead parameters such as mortality, and reduced reliance on subjective parameters associated with morbidity endpoints. Furthermore, creative use of imaging biomarkers allows individual patients to serve as their own control, substantially reducing the number of patients required for statistical significance and the amount of resources expended. Together, these benefits promise to increase trial efficiency and decrease cost, allowing more products to be evaluated with the same resources and making the targeting of less prevalent diseases more economically attractive.

VI. STATUTORY BASIS FOR EMPLOYING BIOMARKERS IN IMAGING

Congress and FDA have recognized the validity of scientifically-appropriate surrogate endpoints in the clinical trial setting as substitutes for traditional trial endpoints. Through the issuance of various rules and regulations, FDA has allowed reliance on surrogate endpoints under limited circumstances in lieu of traditional endpoints, in some cases to speed the regulatory process for certain drugs designed to treat defined illnesses, and in others due to the widespread acceptance of the link between a surrogate endpoint and the clinically-significant endpoint. In addition, Congress has encouraged and expanded the application of surrogate endpoints through provisions in FDAMA. FDAMA and these regulations represent Congress' and FDA's acceptance of surrogate endpoints and provide a strong legal basis upon which to apply imaging biomarkers as surrogate endpoints in the preclinical and clinical trial setting.

A. *Agency Initiatives*

Between 1987 and 1993, FDA implemented various initiatives designed to expedite access to certain drugs for the treatment of serious and life-threatening conditions. Driven largely by the AIDS epidemic, these policies included early access programs and expedited and accelerated review regulations. Notably, there were no explicit provisions or similar programs concurrently established for devices. The significance of these programs lies in their modification of the historic drug regulatory paradigm to compress study timeframes to improve patient access and their reliance on surrogate endpoints to achieve this goal.

Prior to the HIV/AIDS epidemic and its associated agency regulations, FDA recognized a limited number of surrogate endpoints "whereby the efficacy of a drug could be proven by showing an effect on a non-clinically significant endpoint that indicated a likely clinical effect."[42] One example was blood cholesterol level, where a new drug could be approved based on its effects on cholesterol levels rather than on a direct clinical effect such as the occurrence of heart disease. While FDA recognized the applicability of some surrogate endpoints, the agency was conservative as to which surrogates

[42] *See* Nancy K. Plant, *Adequate Well-Controlled Clinical Trials: Reopening the Black Box*, 1-SPG WIDENER L. SYMP. J. 267, 272 (1996).

could be used in lieu of traditional clinical endpoints (e.g., morbidity and mortality), requiring "very good evidence" establishing a link between the clinically significant endpoint and a surrogate.[43]

This conservative approach began to change beginning in the late 1980s as evidenced by various FDA initiatives that broadened the application of surrogate markers through modifications to the existing regulatory approval process. Early access programs, while not explicitly implicating surrogate endpoints, laid the foundation for their broad application through the expansion and codification of procedures that allowed investigational drugs to be distributed outside of traditional clinical trial protocols.

Implemented in 1987, the federal regulation, *Treatment Use of an Investigational New Drug,* or Treatment IND rule, set out to make promising investigational drugs available sooner for treatment purposes for "desperately ill patients as early … as possible," while continuing the formal collection of safety and effectiveness data.[44] Pursuant to this regulation, a drug still under evaluation in clinical trials and not yet approved for marketing could be administered as treatment to patients with a "serious or immediately life-threatening disease," despite an existing lack of proof of safety and effectiveness.[45] The term "immediately life-threatening" is defined as "a stage of a disease in which there is a reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment."[46] Under this regulation, only IND drugs in Phase II or Phase III clinical trials could be used as treatment for a serious or immediately life-threatening disease.[47] Notably, by itself, the term "serious" as used in the regulations was not defined, providing FDA with considerable discretion in deciding what constitutes a condition eligible for early access treatment.[48]

Further expanding on early access initiatives was the 1992 Parallel Track Initiative, designed exclusively for AIDS patients and HIV-related conditions. This initiative established administrative mechanisms to expand the availability of "promising investigational therapies" beyond then-existing IND regulations.[49] Under this policy, access to investigational HIV/AIDS drugs could be authorized as early as Phase I, an expansion of IND regulations that restricted early access to Phases II and III. [50]

Implemented in 1993, Subpart E, *Drugs Intended to Treat Life-Threatening and Severely Debilitating Illness*, codified previously-established FDA procedures designed to expedite the development, review, and marketing phases of new drug and biological products intended to treat serious, life-threatening, or severely debilitating illnesses.[51] These regulations focused on shortening the clinical trial timeframe for gaining FDA approval. For purposes of this regulation, the agency defined "life-threatening" as "diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted; and diseases or conditions with potentially fatal outcomes, where the endpoint of clinical trial analysis is survival."[52] Furthermore, the regulations define

[43] *See* New Drug, Antibiotic and Biological Drug Product Regulations; Accelerated Approval, 57 Fed. Reg. 58,942-44 (Dec. 11, 1992).

[44] 21 C.F.R. § 314.34 (1999).

[45] *See id.* The Treatment IND designation was available provided four criteria were satisfied: 1) the drug is intended to treat a serious or immediately life-threatening illness; 2) there is no existing treatment alternative; 3) the drug is already under investigation; and 4) the drug sponsor is actively seeking drug approval. *Id.*

[46] *Id.*

[47] *See id.*

[48] *See* Greenberg, *supra* note 3, at 319.

[49] *See* Expanded Availability of Investigational New Drugs Through a Parallel Track Mechanism for People with AIDS and other HIV-Related Diseases, 57 Fed. Reg. 13,250 (1992).

[50] *See id.*

[51] 21 C.F.R. § 312.80 (1999).

[52] *See id.*

"severely debilitating" as "diseases or conditions that cause major irreversible morbidity."[53] In light of these definitions and FDA's call for the "broadest flexibility in applying the statutory standards, while preserving appropriate guarantees for safety and effectiveness," the agency expanded the diseases and conditions covered by this regulation with its inclusion of "severely debilitating conditions" as compared to previous regulations.[54] Similar to the early access programs, Subpart E solidified the agency's resolve to make available new drugs and biologics targeting certain conditions and its willingness to alter the regulatory framework as needed, to accomplish this goal.

FDA took its biggest step to date in terms of modifying drug approval standards by embracing surrogate endpoints in its 1992 accelerated approval regulations for new drugs and biologics intended to treat serious or life-threatening illnesses.[55] These regulations explicitly allow for the approval of new drugs and biologics based on "adequate and well-controlled" clinical trials where it is established that the drug or biologic "has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity."[56] Thus, for products designed to treat serious or life-threatening illnesses, surrogate endpoints, in lieu of the traditional endpoints of mortality and morbidity, become available as an option to accelerate the regulatory process.[57] As in previous regulations, safety remained a concern for FDA, and the use of surrogate endpoints necessitated continued research (e.g., postmarket studies of the new drug product following agency approval) to ensure actual clinical benefit.[58]

Perhaps the most significant development in these accelerated approval regulations was the explicit provision of the definition for "seriously." The proposed regulation states that "the seriousness of a disease is a matter of judgment, but generally is based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one."[59] The agency goes on to explicitly include within this definition, Alzheimer's dementia, heart failure, and cancer, as well as some chronic illness such as asthma, rheumatoid arthritis, and depression, thus significantly expanding the number of diseases covered.[60]

B. *Recent Supporting Federal Legislation: FDAMA*

The FDCA underwent substantial revision with FDAMA, legislation enacted as a congressional response to perceived weaknesses in the existing FDA regulatory system, particularly agency approval timeframes.[61] With respect to new drugs, section 112 of FDAMA addresses the accelerated approval of drugs intended to treat serious and life-threatening illnesses, explicitly incorporating the use of surrogate endpoints in clinical trials. In addition, various provisions expand upon the agency's acceptance of surrogate endpoints, adopting a broadly defined scope of their availability and use.[62]

[53] *See id.*
[54] *See id.*
[55] 21 C.F.R. § 314.500 (1999).
[56] *See id.*
[57] *See id.*
[58] *See id.*
[59] *See* New Drug, Antibiotic and Biological Drug Product Regulations; Accelerated Approval, 57 Fed. Reg. 58,942.
[60] *See id.*
[61] *See* FDAMA, Pub. L. No. 105-115, 111 Stat. 2295 (1997).
[62] *See id.*

While FDAMA does not explicitly link surrogate endpoints in the evaluation of medical devices, section 205 introduces the concept of "least burdensome means," a general concept widely believed to encompass the appropriate use of surrogate endpoints in the medical device approval process.

1. *Drug Provisions*

FDAMA section 112 entitled, "Fast Track Products," specifically calls on the Secretary of HHS to "facilitate the development and expedite the review of such drug[s]…intended for the treatment of serious or life-threatening condition[s]…."[63] This language, similar to that found in the accelerated approval regulations, largely codifies existing regulations, designating eligible drugs as "fast track" products.[64] Section 112 also contains a provision calling on the Secretary to establish a program encouraging development of surrogate endpoints that are reasonably likely to predict clinical benefit for serious or life-threatening conditions where there exists the potential to address significant unmet medical needs.[65] Read together, these legislative provisions provide a sound regulatory framework upon which to apply biomarkers in imaging as surrogate endpoints in the preclinical and clinical evaluation of new drugs.

A key element of section 112 is the scope of "fast track" designation, which adopts the broad definition of "serious or life-threatening conditions" found in the accelerated approval regulations. In a House of Representatives Report on section 112, Congress provided guidance as to the criteria to be considered when defining "serious or life-threatening condition" and thus determining the applicability of the "fast track" designation for a specific drug.[66] According to this report, the Secretary should consider such factors as survival, day-to-day functioning, likelihood of disease progression from a less serious one, and chronic illnesses that generally are managed well but that may have serious outcomes.[67] These suggested factors are expansive, allowing for the inclusion of chronic illnesses and day-to-day functional impairments, in practice encompassing virtually any medical condition of consequence.[68] The Senate Labor & Human Resource Committee came to a similar conclusion, finding that the codification of existing regulations broadened their scope, bringing in additional categories of drugs.[69] Importantly, the legislation gives the Secretary of HHS discretion in determining which new drugs are eligible for fast track designation and consequently eligible for the application of surrogate endpoints in clinical trial evaluations.[70]

2. *Device Provisions*

Prior to passage of FDAMA, surrogate endpoints were not outwardly considered in the evaluation of medical devices, as was the case with certain classes of drugs. Even with passage of FDAMA and the strengthening and expansion of surrogate endpoint

[63] *See* FDAMA § 112.

[64] *See id.*; *see also* Greenberg, *supra* note 3, at 345.

[65] *See* FDAMA, Pub. L. No. 105-115, 111 Stat. 2295 (1997); *see also* Greenberg, *supra* note 3, at 344.

[66] *See* H.R. REP. NO. 105-310, at 55 (1977).

[67] *See id.*

[68] *See* FDAMA § 112 (a)(1), 111 Stat. 2309; *see* Deborah G. Parver, *Expediting the Drug Approval Process: An Analysis of the FDA Modernization Act of 1997*, 21 ADMIN. L. REV. 1249, 1261-63 (1999).

[69] *See "Fast Track" Law "Goes Beyond" Accelerated Approval Reg-Senate Cmte.*, F-D-C REP. ("The Pink Sheet"), Aug. 10, 1998, at 7; *see* S. REP. NO. 105-43, at 3.

[70] *See* FDAMA § 112(b)(3), 111 Stat. at 2310.

use with respect to drug evaluation, device regulations still lack an explicit provision for the application of surrogate endpoints. FDAMA section 205 introduces the concept of "least burdensome means," however, and establishes a solid foundation on which to argue their application in device trials.[71]

Section 205 requires the agency to consider the "least burdensome means necessary" for evaluating safety and effectiveness that would have a reasonable likelihood of premarket approval, or demonstrate substantial equivalence in the case of a 510(k) application.[72] While Congress did not explicitly define "least burdensome means," congressional reports, agency guidance, and industry opinion, have led to at least partial consensus on this definition.[73] This consensus maintains that the concept addresses agency efficiency in general, and increased access to new medical technologies in particular, while not altering the agency's statutory requirement that devices be safe and effective for their intended use(s). Accordingly, "least burdensome means" is widely believed to include the appropriate use of surrogate endpoints in preclinical and clinical device trials as such endpoints may be considerably less burdensome than traditional trial endpoints. In fact, the Least Burdensome Industry Task Force, a group of agency and industry officials, in a draft document discussing least burdensome basic concepts and principles de-emphasized the use of the prospective, randomized, well-controlled, double-blind study design as a default for every device submission.[74] Thus, while the "least burdensome means" provision is substantially more general than the supporting provisions for drug evaluations, FDAMA section 205 provides a strong legislative foundation upon which to apply surrogate endpoints, and by extension biomarkers in imaging, in the preclinical and clinical trial setting in the device evaluation process.

VII. DISCUSSION

The FDCA, as amended by FDAMA, clearly recognizes the potential of surrogate endpoints and provides a solid foundation for the use of imaging biomarkers in the evaluation of new drug and device-based medical therapies. Still, these provisions, together with related FDA regulations, do not alter the basic statutory requirement that such therapies be safe and effective for their approved indication(s) and that evidence of this safety and effectiveness be based on sound scientific data. This raises the basic question of how to apply imaging biomarkers in practice to satisfy regulatory requirements while improving the efficiency of medical product evaluation.

To begin, it is imperative to recognize that surrogate endpoints constitute a tool for scientific evaluation, and like any such tool, have promise as well as inherent limitations. Imaging biomarkers are not, and never can be considered, a solution to every preclinical or clinical question. They must be applied in a thoughtful, fully-considered manner by those with experience in their application, so as to ensure, as much as is possible, accurate and complete results. As described in the medical literature,[75] biomarkers in imaging may be used where they are validated for a particular application at issue. Validation may be established where the following criteria are met: 1) the presence of the imaging biomarker is closely coupled or linked with the presence of the target disease or condition; 2) detection and/or quantitative measurement of the imaging biomarker is accurate, reproducible,

[71] *See id.* § 205.

[72] *See id.*

[73] *See generally* John J. Smith & Anne M. Shyjan, *Defining "Least Burdensome Means" Under the Food and Drug Administration Modernization Act of 1997*, 55 FOOD & DRUG L.J. 435 (2000).

[74] THE LEAST BURDENSOME INDUSTRY TASK FORCE, FDA, THE LEAST BURDENSOME PROVISIONS OF THE FDA MODERNIZATION ACT OF 1997: CONCEPTS AND PRINCIPLES (2000).

[75] *See* Smith et al., *supra* note 40, at 633-38.

and feasible over time; and 3) measured changes in the imaging biomarker over time are closely coupled or linked with the success or failure of the therapeutic effect and the true endpoint sought for the medical therapy being evaluated.[76]

An example of this validation process illustrates its utility. CT scans often are used to assess the presence and progression of cancerous tumors. Tumor size is the imaging biomarker, with a reduction in tumor size the desired therapeutic effect, and decreased patient mortality over time the traditional or true endpoint. The presence of tumors can be accurately, reproducibly, and feasibly measured over time, with the reduction in tumor size linked clinically to prolonged survival.[77] CT scans used for tumor size assessment thus meet the validation criteria for an imaging biomarker and may be used with confidence in this role, as it has been for drugs such as trastuzumab (Herceptin®). This same paradigm also may be used to exclude the use of certain imaging findings as biomarkers.

In addition to basic validation, it is important also to consider whether an imaging biomarker captures other crucial considerations of the therapy being evaluated, including side effects and toxicity. Biomarkers that capture therapeutic effects may not assess untoward effects adequately, leading to the possibility of a dangerously incomplete evaluation. Accordingly, such effects must be carefully considered in any instance where biomarkers in imaging are employed. In addition, some biomarkers lack a strong link to the true endpoint, providing reliable, but incomplete data. For example, measurement of bone mineral density via bone densitometry provides reliable information about changes that occur as a response to treatments for osteoporosis. This biomarker does not provide information about architecture and bone strength, however, making it a poor and incomplete biomarker without a solid link to the true endpoint.

While the statutory basis for, and historical use of, surrogate endpoints is developed more fully in the drug model, the use of surrogate endpoints in the clinical evaluation of medical devices offers many of the same advantages over reliance on the prospective, randomized, well-controlled study and traditional endpoints. For example, devices routinely are used for off-label indications over the course of many years, making the conduct of clinical evaluations to validate those indications, which have become the standard of care, difficult. Use of validated imaging biomarkers under these circumstances can address some of the technical and ethical challenges of reference standard trials and can provide data on the clinical benefit of these devices for the non-FDA approved indications. Beyond this, and unique to the evaluation of genuinely new devices as opposed to drugs, the prospective, randomized, well-controlled study design oftentimes is difficult or not feasible due to the inherent challenge of blinding patients and physicians when a medical device is to be deployed or implanted. Under these circumstances, the use of biomarkers in imaging can enhance the availability of meaningful evidence in the evaluation of a medical device's safety and effectiveness when alternative clinical study designs are necessary.

Ultimately, use of imaging biomarkers and other surrogate endpoints for drugs and devices most likely will be accepted by scientists and regulators when they are well-studied and characterized in large groups of patients, as such studies are likely to minimize the possibility of unexpected and inaccurate results that may result with limited experience

[76] A. Schatzkin & M. Gail, *The Promise and Peril of Surrogate Endpoints in Cancer Research*, 2 NATURE REV. CANCER 19-27 (2002); R.L. Prentice, *Surrogate Markers in Clinical Trials: Definitions and Operations Criteria*, 8 STAT. MED. 431-40 (1989); T.R. Fleming & D.L. DeMets, *Surrogate Endpoints in Clinical Trials: Are We Being Misled?*, 125(7) ANN. INT. MED. 605-13 (1996).

[77] M. Buyse et al., *Relation Between Tumor Response to First Time Chemotherapy and Survival in Advanced Colorectal Cancer: A Meta-Analysis* 356 LANCET 373-78 (2000).

with a given surrogate endpoint. This reality, coupled with the relatively high expense of completely validating any given imaging biomarker, may make it relatively unattractive for a single sponsor to fully assume the cost of biomarker validation. Given the widespread use of medical imaging in a wide variety of clinical settings, however, there already is a vast amount of imaging biomarker data, albeit in unprocessed form, already gathered and theoretically available for analysis. At least one academic organization has recognized the potential of this existing knowledge, and is working with FDA and industry to identify and develop this untapped resource.[78] Still, it is uncertain how this and other private efforts directed at developing biomarkers in imaging can reach their full potential without the active and involved leadership of government, particular FDA.

Even where imaging biomarkers are not presently fully developed, such surrogate endpoints still may have utility outside of the formal regulatory decisionmaking process. Specifically, biomarkers lacking full validation may be used internally by sponsors for go/no go decisions, or as a secondary endpoint in clinical trials where traditional endpoints are primary. In either case, any accumulated data could further support use of the imaging biomarker in future work, particularly if developing such surrogates becomes an FDA priority.

VIII. CONCLUSION

There is no doubt that establishing the safety and effectiveness of tomorrow's new drug and device-based therapies will continue to be a lengthy and costly exercise. The appropriate use of imaging biomarkers, recognized by scientists and industry researchers as suitable clinical trial endpoints offers the promise of improving the efficiency of the current medical product evaluation process while maintaining the safety and effectiveness standards established by the FDCA. The FDCA, as amended, as well as applicable FDA regulations, supports the responsible use of imaging biomarkers. It is up to FDA, regulated industry, and the medical community to work together to ensure that this promise is fully realized on both the drug and medical device fronts.

[78] This organization is the Massachusetts General Hospital Center for Biomarkers in Imaging. Information about the Center can be found at http://www.biomarkers.org.