Evaluating Oversight of Human Drugs and Medical Devices: A Case Study of the FDA and Implications for Nanobiotechnology

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This article evaluates the oversight of drugs and medical devices by the U.S. Food and Drug Administration (FDA) using an integration of public policy, law, and bioethics approaches and employing multiple assessment criteria, including economic, social, safety, and technological. Throughout, assessments employing both the multiple criteria and a method of expert elicitation are combined with the existing literature, case law, and regulations providing an integrative historical case study approach. The goal is to provide useful information from multiple disciplines and perspectives to guide discussions regarding appropriate oversight frameworks for nanobiotechnology applications under the FDA's purview.

The criteria we use for the assessment of oversight were developed through a multi-stage process. The first stage involved consultation of the legal, ethics, and public policy literature regarding oversight and collection of relevant written materials that address criteria utilized in oversight analysis. Searches were conducted using a variety of databases and resources.[1] We refined these criteria and our vision of their relationships by consulting the literature on oversight analysis, through an expert elicitation process described elsewhere,[2] and by consensus among the project investigators. The criteria chosen fell into four groups: (1) those associated with the development of an oversight system (e.g., establishment of policies, procedures, or regulations); (2) the attributes of an oversight system (e.g., how the system operates for particular processes or decisions); (3) the outcomes of an oversight system (e.g., economic, health, safety, and environmental impacts); (4) and the evolution of an oversight system (i.e., changes to the development, attributes, or outcomes over time). (See Appendix A in the Comparative Report for a full list of criteria).[3] Our methodology is described elsewhere in the literature.[4]

This article uses the assessment criteria and expert elicitation findings as tools to assess FDA oversight of drugs and devices and to derive lessons for effective oversight and regulatory mechanisms for nanotechnology. Section I describes nanotechnology in human

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drugs and medical devices and the state of oversight for those products regulated by the FDA. Section II describes the results of our expert elicitation research. Section III focuses on key criteria and ties them to the current literature and larger debate regarding regulation of human drugs and medical devices. We conclude with lessons for the oversight of nanobiotechnology.

I. The Food and Drug Administration: Oversight Mechanisms

A. A Short History of FDA Oversight of Human Drugs and Medical Devices

The FDA historically has operated through a number of specialized federal agencies at different points in its history. Beginning in 1883, the U.S. Department of Agriculture (USDA) established the position of Chief Chemist of the Bureau of Chemistry.[5] 1906 marked the beginning of the modern era of drug regulation with the passage of the first comprehensive federal food and drug law, which was enforced by the Bureau of Chemistry until 1927. In 1927, authority to enforce the 1906 Act was transferred to the newly formed Food, Drug, and Insecticide Administration (FDIA). The FDIA was renamed in 1931 as the FDA under the direction of Walter G. Campbell, the first official commissioner.[6] In 1938, Congress passed the Federal Food, Drug and Cosmetic Act (FDCA).[7] Key modern amendments related to drugs and devices occurred in 1962, 1976, 1997, and 2007. Throughout this article, the acronym FDA will refer to the current agency as it has evolved from these previous agencies, bureaus, and individuals to enforce the 1906 Act and subsequent statutes and amendments.

The FDA is one of eleven agencies in the Department of Health and Human Services[8] and is tasked with enforcing over 45 federal statutes with products accounting for about 25% of consumer spending in the U.S., including 80% of the national food supply and all cosmetics, vaccines, drugs, medical devices, tissues for transplantations, and equipment that emits radiation.[9] This amounts to over $1.5 trillion annually in consumer goods.[10] The broad duty of the FDA in overseeing consumer products is articulated in its mission statement:

> The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation. The FDA is also responsible for advancing the public health by helping to speed innovations that make medicines and foods more effective, safer, and more affordable; and helping the public get the accurate, science-based information they need to use medicines and foods to improve their health.[11]

Legal oversight of human drugs has a long history, dating back to the original Pure Food and Drugs Act of 1906 (1906 Act). The 1906 Act has been described as the most far-reaching of its kind with no comparable antecedent regarding human health and welfare.[12] Medical device provisions are grounded in the original and subsequent drug regulation provisions, although they differ now from the drug provisions in using a classification system based on degree of risk. Over the course of the 100-year history of FDA drug oversight and almost 70 years of device oversight, definitions have been expanded and added, provisions adjusted, and new centers and guidance created to fill gaps in oversight and account for new developments.

Drugs and devices are contained in Chapter 5 of the current iteration of the FDCA. In addition to setting out legal requirements, the FDCA authorizes agency rulemaking,[13] which gives the FDA the authority to set rules to implement and explain the provisions of the FDCA. There are also FDA guidance documents, policy statements and manuals, formal and informal statements and advice provided by the FDA, and various publications that provide procedural advice such as press releases, public service announcements, and enforcement reports.

This article uses the assessment criteria and expert elicitation findings as tools to assess FDA oversight of drugs and devices and to derive lessons for effective oversight and regulatory mechanisms for nanotechnology.

Human drugs and medical devices are the two consumer product areas most heavily regulated by the FDA throughout the pre- and post-marketing phases, although the extent of regulation varies depending on a number of factors, as discussed below. Relevant definitions for drugs and devices are provided in Figure 1.[14] Products that consist of a combination of drugs, devices, and/or biologics are regulated based on their primary mode of action. Figure 1 includes the definition of biologics in order to distinguish from new drugs; a biologic is derived from a living source rather than chemically synthesized. Biologics provisions

are contained within the Public Health Service Act (PHSA), which makes biologics subject to the FDCA.[15] We mention these provisions and identify biologics as relevant in the discussion of nanodrugs and nanodevices because emerging combination products utilizing nanotechnology may contain a biologic, such as a drug-biologic or device-biologic.

NEW HUMAN DRUGS AND THE NDA PROCESS

The FDA has authority to regulate human drugs under the FDCA.[16] Regulation of human drugs includes manufacturing controls for quality purposes, labeling controls for consumer protection, and a premarket approval process for new drugs to determine safety and efficacy using a risk-benefit approach.[17] The Center for Drug Evaluation and Research (CDER) is responsible for the evaluation of safety and efficacy of brand name and generic prescription and over-the-counter (OTC) drugs, advertising of prescription drugs, and post-market monitoring of drug products for risks and adverse events.

Over time, a number of regulatory routes to market for human drugs have developed. These include new drug applications (NDAs), abbreviated new drug applications (ANDAs) (generally for generic drugs),[18] OTC applications, and biologics license applications (BLAs) for biological products.[19] The NDA route is most relevant to nanodrug oversight and is addressed below. Throughout this article, the oversight of human drugs will generally refer to the oversight of new drugs via the NDA process.

There are a number of well-defined pre-approval phases in bringing a new drug to market. The first is the preclinical investigation phase (consisting of labo-

Figure 1

Food, Drug and Cosmetic Act Definitions

Drug:	"(A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clause (A), (B), or (C)." (21 U.S.C § 321(g)(1))
New drug:	any drug "not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling,…" (21 U.S.C. §321(p)(1)) OR which "has become so recognized, but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions" (21 U.S.C. § 321(p)(2))
Medical device:	an "instrument, apparatus, any component, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component part, or accessory, which is -- (1) recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them, (2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or (3) intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes." (21 U.S.C. § 321(h))
Biologic:	"a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings" (42 U.S.C. § 262(i))
Combination product:	a single product containing both a drug and a medical device, a drug and a biologic, and medical device and a biologic, or all three; CDER, CBER, and CDRH categorize and review combination products according to the primary mode of action (*e.g.,* a product with the PMOA of a drug is classified as a drug). (21 C.F.R. § 3.2 (e))

ratory and animal testing). This preclinical phase does not require prior notification of the FDA, but studies must follow good laboratory practices.[20] Upon successful completion of preclinical testing, an investigational new drug application (IND) must be filed prior to initiation of clinical trials, including a general investigative plan; clinical trial protocols; information on proposed drug chemistry, pharmacology, toxicology, and manufacturing and controls; and a summary of previous human experience with the drug.[21]

The clinical trial phase collects safety and efficacy information. Trials must conform to informed consent[22] and Institutional Review Board (IRB) requirements.[23] There are three key phases to the clinical trials. Phase 1 typically involves approximately 20-80 healthy test subjects or patients to determine metabolism, pharmacologic action, and side effects. Phase 2 involves up to several hundred patients with the disease or condition under study and should obtain initial evidence of effectiveness against the targeted disease, explore further risks and side effects, and confirm preliminary data on optimal doses. Phase 3 involves thousands of people at many different locations and can be initiated after appropriate notification to FDA and gathering of preliminary efficacy data. The primary goal is to collect data necessary to meet safety and efficacy standards required for FDA approval. In addition to these 3 phases of the clinical trials, the FDA can require the sponsor to undertake post-approval Phase 4 studies in order to secure further data.

Throughout the clinical trial phases, sponsors and investigators have obligations. These include the following: obtaining valid informed consent; ensuring patient safety; assuring appropriate scientific conduct; keeping the FDA informed; selecting appropriate investigators; adhering to protocols; maintaining accurate and up-to date records; engaging in appropriate shipping and handling of products; and reporting adverse events. Violation of any of these can lead to FDA action, including a hold on clinical trials and withdrawal or suspension of the IND. Following completion of clinical trials, the sponsors will prepare an NDA seeking FDA approval for a specific indication(s), which must be approved before the drug can enter the market.[24] The applicant must include the following: preclinical data; human pharmacokinetic and bioavailability data; clinical data, which must include adequate tests to demonstrate that the drug is safe under the proposed conditions and substantial evidence that the drug is effective; substantial evidence of efficacy, generally consisting of at least two adequate and well controlled studies;[25] a description of proposed methods of manufacture; a description of the drug product and drug substance; a list of each patent claiming the drug, drug product, or method of use; the drug's proposed labeling; and a summary of the application, including risks and benefits of the new drug.[26]

There are also provisions allowing expedited approval for certain types of new drugs. These provisions include accelerated approval (Fast Track) and treatment INDs. Fast Track approval is available for life-saving treatments, and is used particularly for approval of cancer drugs. Treatment INDs enable the use of an investigational drug outside of clinical trials in order to treat patients with serious or immediately life-threatening diseases for which no comparable or alternative therapy is available.

Surrogate endpoints are another mechanism of flexibility in new drug approval.[27] The use of surrogate endpoints is beneficial when clinical trials would otherwise be dangerous to patients or take an impractically long time to complete. For example, CD4 cell counts may be used as a surrogate endpoint in clinical trials for AIDs products, and serum cholesterol levels may be used for hypercholesterolemia. However, this approach involves assumptions about the adequacy of the endpoint to signal safety and efficacy.

A new drug may also be approved under the abbreviated new drug application (ANDA) process. Requirements include the following: showing that the proposed conditions of use for the drug have previously been approved for a drug that is already FDA approved for safety and efficacy; that active ingredients are the same as in the already-approved drug; that the generic drug will use the same route of administration, dosage form, and strength of the approved drug (the FDA will accept differences if they will not affect safety or efficacy, but the applicant must first file a "suitability petition"); that the generic drug is bioequivalent to the listed reference drug;[28] that the proposed generic labeling is the same as the labeling approved for the approved drug; basic technical information required of a full NDA, including a list of components, statement of the composition of the drug, and a description of the methods and facilities used in production; samples of the generic product and proposed labeling; and certification informing FDA of the patent status of the listed reference drug relied upon by the ANDA.[29]

MEDICAL DEVICES

The FDA also has authority over medical devices under the FDCA. The Center for Devices and Radiological Health (CDRH) oversees medical devices and radiation-emitting products. Similar to drug oversight, FDA regulation of medical devices has evolved in response to rapid technology advances yet in a much shorter window of time than that of drug regulation.

Regulation of medical devices with any significant approval, monitoring, and enforcement powers began with the Medical Device Amendments (MDA) in 1976, which created a tiered regulatory scheme operating on perceived level of risk, based on prior experience with a type of device or mode of action.[30] Between 1938 and the 1976 amendments, devices were subject merely to misbranding and adulteration provisions as set out in the original food and drug provisions in 1906. Devices that were developed prior to the enactment of the MDA were generally grandfathered in, so that no FDA clearance or approval is required. Beginning in 1976, expert scientist and medical device specialist advisory panels were established to categorize products into Class I-III; this took until 1988 to complete.[31]

Devices are divided into Class I-III based on the nature and degree of risk.[32] Class I devices are the lowest risk, subject typically to "general controls" which consist of facility registration and product listing with FDA, record maintenance and filing of marketing reports, adherence to good manufacturing procedures (GMPs) and quality system registrations (QSRs), and any distribution and use limitations imposed by FDA.[33] Certain Class I "reserved devices" that pose more than minimal risk are put through the 510(k) process described below.[34]

Class II devices pose an increased, moderate risk and are subject to special controls, including postmarket surveillance studies, patient registries, mandatory performance standards, and adherence to specific FDA guidelines.[35] Product clearance is required for most Class II devices; some Class II devices are exempt as classified in the *Federal Register*.[36] This clearance process is commonly called the "510(k)" process in reference to the section number in the FDCA. Under the 510(k) process, the FDA determines that a device is "substantially equivalent" if it (1) has the same intended use and the same technological characteristics of an existing device or (2) has the same intended use and different technological characteristics but the information submitted to FDA does not raise new questions of safety and efficacy and demonstrates that the device is at least as safe as the legally manufactured device.[37] Class II 510(k) cleared devices do not mandate a drug-like clinical trial and premarket approval (PMA) process as is required for Class III highest risk devices. The average review time for a 510(k) submission is approximately three months.[38]

Class III is the highest risk classification, requiring a PMA filing prior to marketing in the United States (unless it is a product amenable to the 510(k) process). The established device classifications that manufacturers can use as the basis for a 510(k) application are listed in the *Code of Federal Regulations*.[39] If a new device has the same intended use and meets the general description of the device in the classification, then the new device will fall under that regulation scheme. If the device is not currently listed, it will be considered a Class III device and subject to premarket approval requirements until the FDA determines otherwise.

Increasingly, products combine drugs, devices and biologics into a single product.

High-risk Class III products such as heart valves, implantable cardioverter defibrillators (ICDs), and pacemakers must be approved via the PMA process.[40] Class III products are devices that are life-sustaining, life-supporting, and often implantable, plus any new devices that are not substantially equivalent to marketed devices.[41] Generally these products must first complete clinical testing under an investigational device exemption (IDE), which is conceptually similar to the IND in the drug world but generally involves fewer participants and simpler trials.[42] The PMA lists uses and indications of the specific product, warning and contraindications, product labeling, results of clinical trials, and manufacturing processes information.[43] This gives the FDA information in order to assess risks and benefits, as well as to determine uses for the device. Class III devices comprise about 10% of medical devices,[44] and the average review time for a PMA is approximately 8.5 months.[45]

Each year, an average of 8,000 new medical devices enter the U.S. market, with between 50-80 channeled through the Class III PMA process; approximately 3,500 channeled through the 510k premarket notification process for Class II and select Class III devices; and approximately 4,000 channeled through the Class I process.[46] The 510(k) process is much less expensive and laborious for applicants than the PMA process, mainly because it does not usually require clinical research.[47] Clinical studies for a Class III medical device can take 4-5 years and cost between $15-20 million.[48]

COMBINATION PRODUCTS

Increasingly, products combine drugs, devices and biologics into a single product. It was originally unclear how these "combination products" should be regulated. The 2002 Medical Device User Fee and Modernization Act[49] created the Office of Combina-

tion Products (OCP) and assigned primary regulatory responsibilities and oversight spanning the regulatory life of drug-device, drug-biologic, and device-biologic products to CDER, CBER, and CDRH based on the "primary mode of action" (PMOA). PMOA is defined as "the single mode of action of a combination product that provides the most important therapeutic action of the combination product."[50] Mode of action is defined as "the means by which a product achieves its intended therapeutic effect or action" where "'therapeutic' action or effect includes any effect or action of the combination product intended to diagnose, cure, mitigate, treat, or prevent disease, or affect the structure or any function of the body."[51] A biological product mode of action is chiefly defined by whether it "acts by means of a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product"; a device mode of action is characterized as not having a biological product mode of action and not achieving "its primary intended purposes through chemical action"; and a drug mode of action is characterized as not having either a biological product or device mode of action. The divide thus between a drug and a device has effectively been interpreted as the difference between chemical and mechanical action, where every medical product that does not act chemically to reach its intended effect is regulated as a medical device.[52]

B. Nanotechnology in Human Drugs and Medical Devices

Nanotechnology has the potential to provide tools for in vitro and in vivo diagnostics for much earlier detection of disease; facilitate targeted drug delivery and regenerative medical applications; supply antimicrobial coatings for implanted medical devices; and enable devices that seek, bind to, and destroy tumor cells. Nanobiotechnology has been defined as "a field that applies the nanoscale principles and techniques to understand and transform biosystems (living or non-living) and which uses biological principles and materials to create new devices and systems integrated from the nanoscale."[53]

In a 2007 *Nature Materials* editorial, authors found as many as 207 companies developing nanomedicine projects, accounting for as much as $6.8 billion in sales in 2004 alone.[54] An industry source reports that between 2005 and May 2007 over 130 nanotech-based drugs and delivery systems and 125 devices or diagnostic tests were in clinical, pre-clinical, or commercial development.[55] The market is projected to grow to about $12 billion by 2012.[56] Current research activity is dominated by development of drug delivery applications, accounting for about three-quarters of this emerging market.[57]

The FDA, as the gatekeeper to clearance and approval of medical and health care products in the United States, will be largely responsible for the oversight of the clinical research, approval, and marketing of nanotechnology products for human use. At present, nanotechnology products are assessed on a case-by-case basis using existing regulations without specific categories, requirements, or processes applicable to nanotechnology. The FDA is reviewing and has approved human drug and medical devices that classify as "nanoproducts" using the established oversight paths for drugs and devices.[58] We provide an overview of drug and device nanobiotechnology products both on the market and in development in another publication.[59] These include the anti-cancer drugs Abraxane®[60] and Doxil,®[61] Rapamune® immunosuppressant for prevention of organ rejection in renal transplant patients,[62] Epaxal® Hepatitis A vaccine,[63] Estasorb topical estrogen therapy,[64] Vitoss® bone graft substitute,[65] TiMesh tissue reinforcement,[66] EnSeal™ tissue sealing system for laparoscopic surgery,[67] and CellTracks® Analyzer II in vitro diagnostic device.[68]

The FDA has created a Nanotechnology Task Force to tackle specific ongoing issues with regard to nanotechnology. Their July 2007 report concluded that a new regulatory framework or special regulations for nanotechnology were not necessary at that time, but the agency must keep abreast of the science in order to appropriately apply regulations in the future.[69] The report flagged combination products as potentially problematic, acknowledging novel issues for regulation:

> The very nature of nanoscale materials — their dynamic quality as the size of nanoscale features change, for example, and their potential for diverse applications — may permit the development of highly integrated combinations of drugs, biological products, and/or devices, having multiple types of uses, such as combined diagnostic and therapeutic intended uses. As a consequence, the adequacy of the current paradigm for selecting regulatory pathways for 'combination products' may need to be assessed to ensure predictable determinations of the most appropriate pathway for such highly integrated combination products.[70]

While the creation of the OCP has resulted in a more collaborative approach to regulating emerging medical products crossing traditional boundaries between drugs, medical devices, and biologics, the rapidly developing applications in nanomedicine that

merge drug delivery and diagnostics may pose the next challenge. At the nanoscale, the distinction between chemical and mechanical action are not easily distinguishable.[71] While it is not so critical in a scientific sense how a nanotechnology product works (chemically or mechanically), it becomes extremely important for legal and regulatory purposes.

Overarching issues for nanobiotechnology oversight include the role of FDA regulation, the need for proactive guidance, the adequacy of the current regulatory system, classification problems, and questions of whether nanoproducts are new chemical entities or new medical devices requiring heightened review. The remainder of this article describes expert elicitation and assessment criteria utilized to identify important concepts and themes from drug and medical devices to apply to the development of oversight of nanobiotechnology products in these realms.

II. Expert Elicitation

In order to glean lessons from oversight of drugs and medical devices to inform the discussion of possible future oversight of nanotechnology products by the FDA, we conducted targeted expert elicitation using 28 criteria. These criteria and the corresponding label used throughout the remainder of this article are provided in Figure 2. The categorized criteria fall into four groups: (1) those associated with the initial or continuing development of an oversight system (e.g., establishment of policies, procedures, or regulations); (2) the attributes of an oversight system (e.g., how the system operates for particular processes or decisions); (3) the outcomes of an oversight system (e.g., social, economic, cultural, health, environmental, and consumer impacts); and (4) the evolution of an oversight system (e.g., changes to the development, attributes, or outcomes over time). These four groups are denoted in the criteria labeling as "D" (7 criteria), "A" (15 criteria), "O" (5 criteria), and "E" (one criterion).

We describe results of this expert elicitation below in the remainder of Section II. These criteria and expert elicitation results are then grounded to existing literature, case law, and regulations in Section III, using a historical, case studies approach. The goal is to provide useful independent, analytical information from multiple disciplines and perspectives to guide discussions regarding appropriate oversight frameworks for nanotechnology applications under the FDA's purview.

A. Methodology

DATA COLLECTION

We collected surveys from 15 experts regarding their opinions on the set of 28 criteria regarding oversight of drugs and medical devices. These experts were identified based on several factors including their contributions to the scientific literature, membership on advisory boards and/or editorial committees of key journals, and status within their respective communities. A total of 31 such experts were approached with backgrounds spanning a variety of fields including engineering, public policy, public health, law and medicine.

The expert elicitation was performed using a survey sent by email. The Drug and Medical Device Expert Elicitation Survey Instrument is available at <http://lifesci.consortium.umn.edu/publications/research_pubs>. Experts were provided with these instructions: "On a scale of 1 to 100…please evaluate how the U.S.

Figure 2
Project Criteria Labels and Descriptions

Label	Criteria Description
D1	Impetus
D2	Clarity
D3	Legal grounding
D4	Public input
D5	Transparency
D6	Financial resources
D7	Empirical basis (development)
A8	Legal grounding
A9	Data requirements and stringency
A10	Post-market monitoring
A11	Treatment of uncertainty
A12	Empirical basis (attributes)
A13	Compliance and enforcement
A14	Incentives
A15	Treatment of intellectual property
A16	Institutional structure
A17	Flexibility
A18	Capacity
A19	Public input
A20	Transparency
A21	Conflict of interest
A22	Informed consent
E23	Extent of change
O24	Public confidence
O25	Research and innovation
O26	Health and safety
O27	Distributional health impacts
O28	Environmental impacts

human drug oversight system and/or the medical device oversight system performs with regard to each criterion based on the example interpretation posed." The response scale was divided into five ranges: 1-20 (improbable, probably not, unlikely, near impossibility), 21-40 (less than an even chance), 41-60 (even chance), 61-80 (probable, likely, I believe), and 81-100 (near certainty, virtually certain, highly likely). Experts were asked to provide two ratings for each criterion in separate columns: one for the oversight of drugs and one for the oversight of devices. Instructions also specified "[f]or consistency in answering each question for drugs and medical devices, please tailor your opinion on new drug applications and newly-developed devices (Class II or III)."

We received a total of 15 completed surveys (giving a response rate of 48%); 14 completed the survey for both drugs and medical devices and 1 completed the survey for drugs only. A few respondents provided handwritten comments on specific criteria. The respondents were classified into one of four categories based on their self-reported institutional affiliation: industry, academic, non-governmental organization (NGO)/non-profit organization, and government. This information is provided in Figure 3 below. Our data includes 1 government, 2 industry, 3 NGO/non-profit and 9 academic experts. One NGO/non-profit expert responded only to the drug survey instrument.

DATA ANALYSIS

Statistical analysis of the data was performed using Matlab 7.0 software. Identical, separate analyses were carried out for both the drugs and devices categories. For each criterion the mean score, median score, standard deviation and number of responses (n) was found, and a 10-bin histogram was created. The 10 bins of the histograms each spanned a score range of 10 points, i.e., 1-10, 11-20, 21-30, ... , 91-100. Responses for each criterion were sorted into appropriate bins, and each bin was examined to classify responses according to the 4 types of experts. The histograms were developed in stacked form so that the number of each type of expert within each bin could be easily examined.

The Pearson correlation coefficient (r) between each pair of criteria as well as the corresponding p-value was calculated using the intrinsic Matlab function "corrcoef." The equation used by the "corrcoef" function to determine the value of r is shown below. In this equation, sigma represents the standard deviation and C is the covariance matrix. C(i,j) is the element of the covariance matrix located at the intersection of the "i" row and the "j" column, which represents the covariance between the "i" and "j" numbered criteria.

Figure 3

Expert Experience and Affiliation

All expert information is self-reported in responding to the survey instrument.

Education	Professional Experience	Current Institutional Affiliation
MD, PhD	Medicine	Industry
BA, MA, PhD	Public Policy	Academic
PhD	Engineering	Academic
BS, PhD	Science, Engineering	Academic, prior industrial employment
PhD	Science	Academic
No response	Law, Industry	Industry, Academic
JD	Law, Public Policy	Other: Non-Profit Public Interest Org
MA, JD	Law, Public Policy	Academic
BA, JD	Law	Other: Public Interest Law
BA, JD	Law, Public Policy	Other: Legal Profession; Gov't Agencies
MD, MBA	Medicine	Academic
BA	Medicine, Public Policy	Other: Non-Profit Agency
BA, JD	Law	Academic
JD, MPH	Law, Public Health	Academic
JD, PhD	Law	Academic, Other: of-counsel at law firm

$$R(i,j) = \frac{C(i,j)}{\sqrt{C(i,i)C(j,j)}} = \frac{C(i,j)}{\sigma_i \sigma_j}$$

A cutoff of r=0.7 or, equivalently, r^2=0.49 was chosen as a minimum for determining "significant" correlations. This information enabled the construction of influence diagrams which show pairs of criteria that are significantly correlated, with the color of the line indicating the strength of the correlation according to the key shown.

LIMITATIONS OF THE STUDY

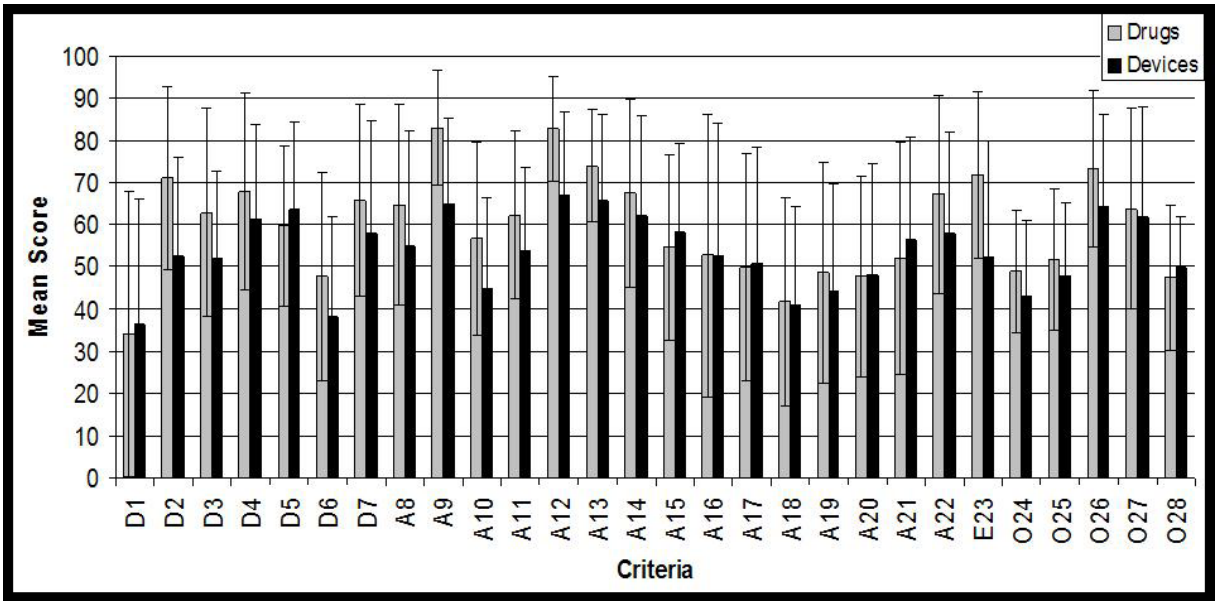
It is important to point out the limitations of our study and emphasize that the data is being used to examine the FDA oversight of drugs and devices rather than as definitive data to support or refute a particular hypotheses regarding the criteria. Stated differently, our results are not conclusive evidence of any particular attribute or outcome of the oversight system, but for use as a tool to frame the article and tie in existing literature and debate in this area. Study limitations include the small sample size, the selection process for experts, the extensive time frame of FDA oversight, the substantial variation in the regulatory system even within drugs and devices, personal differences among experts as to quantification of a particular criterion, and our use of results to frame "strengths" and "weaknesses" of each system.

There was also variance in responses to a number of criteria. The number of respondents ranged from 11-15 for any given criterion within the survey instrument and as noted previously, one expert answered only for drugs. This sample size is fairly small, although the use of similar sample sizes is supported in the literature for expert elicitation.[72] Because of the small sample size, these results are specific to the perspectives and opinions of these 15 experts. We do not attempt to extrapolate from these results. If even two experts were removed from the pool, the results would likely change. Given the selection process of experts, there was potential selection bias, as experts were chosen non-randomly by project members based on their contributions to the scholarship and debate in the area of drugs and devices. There is also an uneven distribution of affiliation of respondents. The disproportionate number of experts that classified themselves as academics compared to the very limited number of government, NGO/non-profit, and industry respondents makes comparisons by expert affiliation difficult.

The survey instrument may also be limited in the fact that there was no specific time frame reference. Provisions of the FDCA have been in effect for over 100 years and its substantive requirements have changed over time. Experts likely struggled with linking their

Figure 4

Calculated Values for Means and Standard Deviations for All 28 Criteria for Drugs and Devices



responses to a particular time period. A few experts provided feedback that this was indeed a challenge.

Experts were asked to assign a number for each oversight criterion, quantifying answers using descriptive phrases to translate between the scale provided and common phrases. However, respondents were informed that they "[did] not have to refer to these phrases at all, and can enter your scores directly based on your own interpretation of the criteria." In addition, there is ambiguity in interpreting scores; should a score of 50 be interpreted to mean that the expert felt neither one way nor the other, or that the expert was unsure about their answer? This distinction cannot be distilled from analysis of the data.

Finally, we are subjectively defining "strengths" and "weaknesses" of the systems. In some cases, what we describe as a "weakness" may be perceived by others as a strength of the system, or a positive policy outcome; likewise, a "strength" may be considered a weakness by others, and thus negative policy outcome.

B. Results

OVERVIEW

Initial data analysis consisted of calculating the means, medians, and standard deviation for responses on each of the 28 criteria for both drugs and medical devices. Figure 4 provides an overview, depicting only the means and standard deviations. Figures 5 and 6 show all calculated values as well as the number of experts (N) who responded. The mean values ranged from 34.2 (D1 – drugs) to 83.0 (A9 – drugs), while the standard deviations were between 11.8 (O28 – devices) and 33.8 (D1 – drugs).

CONSENSUS AMONG EXPERTS

In order to ascertain whether there were certain criteria on which experts agreed for the most part, we looked at the data for patterns of agreement. We defined and examined agreement in three ways: (1) comparing the standard deviations (i.e., which values fell below the average standard deviation, where

Figure 5

Drugs Statistics

Criteria	Mean	Median	Std Dev	N
D1	34.2	20	33.8	15
D2	71.1	80	21.7	14
D3	62.9	70	24.7	14
D4	67.9	72.5	23.3	14
D5	59.6	50	19.1	14
D6	47.7	50	24.6	13
D7	65.8	70	22.7	13
A8	64.7	70	23.9	15
A9	83.0	90	13.6	15
A10	56.7	60	22.8	15
A11	62.3	60	20.0	13
A12	82.9	80	12.5	15
A13	74.0	75	13.4	15
A14	67.5	70	22.4	14
A15	54.6	50	21.9	13
A16	52.7	65	33.5	15
A17	49.9	50	26.8	15
A18	41.7	40	24.6	15
A19	48.7	50	26.1	15
A20	47.7	50	23.7	15
A21	52.1	60	27.5	15
A22	67.1	77.5	23.6	14
E23	71.7	70	19.8	15
O24	49.0	50	14.4	15
O25	51.7	50	16.7	15
O26	73.3	80	18.7	15
O27	63.7	65	23.8	15
O28	47.5	50	17.1	12

Figure 6

Devices Statistics

Criteria	Mean	Median	Std Dev	N
D1	36.4	30	29.6	12
D2	52.5	50	23.4	12
D3	52.1	55	20.6	12
D4	61.3	65	22.7	12
D5	63.8	60	20.6	12
D6	38.0	40	23.9	12
D7	57.9	60	26.8	12
A8	55.1	70	27.3	13
A9	65.0	75	20.2	13
A10	44.6	50	21.7	13
A11	53.8	50	19.9	12
A12	66.9	70	19.8	13
A13	65.8	70	20.5	13
A14	62.3	70	23.5	13
A15	58.3	60	20.8	12
A16	52.7	50	31.5	13
A17	50.7	50	27.7	13
A18	40.8	30	23.5	13
A19	44.2	40	25.3	13
A20	48.1	50	26.4	13
A21	56.5	60	24.1	13
A22	58.1	60	24.0	13
E23	52.3	50	27.5	13
O24	43.1	40	17.9	13
O25	47.7	50	17.4	13
O26	64.2	70	22.0	13
O27	61.9	60	26.1	13
O28	50.0	50	11.8	11

a below-average standard deviation indicated agreement); (2) classifying responses numerically into three bins, labeled "low" for a score of 1-30, "medium" for a score of 31-70, or "high" for a score of 71-100, then determining which criteria had a high concentration of scores in one bin and using that as an indication of agreement; and (3) qualitative visual assessment (i.e., assessing whether the histograms showed agreement among the experts). Examples of histograms that were taken to show "low," "medium," and "high" agreement are shown below in Figure 7. In the high-agreement example the scores are mostly grouped in the highest three bins ranging from 71-100, with only a few outlying responses. In the medium-agreement histogram the overall range of scores was broader, spanning from the very lowest to very highest bin. Finally, in the low-agreement histogram, the scores cover a broad range and there is no one region where the scores are noticeably concentrated.

This analysis was done for both drugs and devices and the results were organized into chart form in Figures 8 and 9. Entries that are shaded in gray indicate consensus as defined in each of three ways.

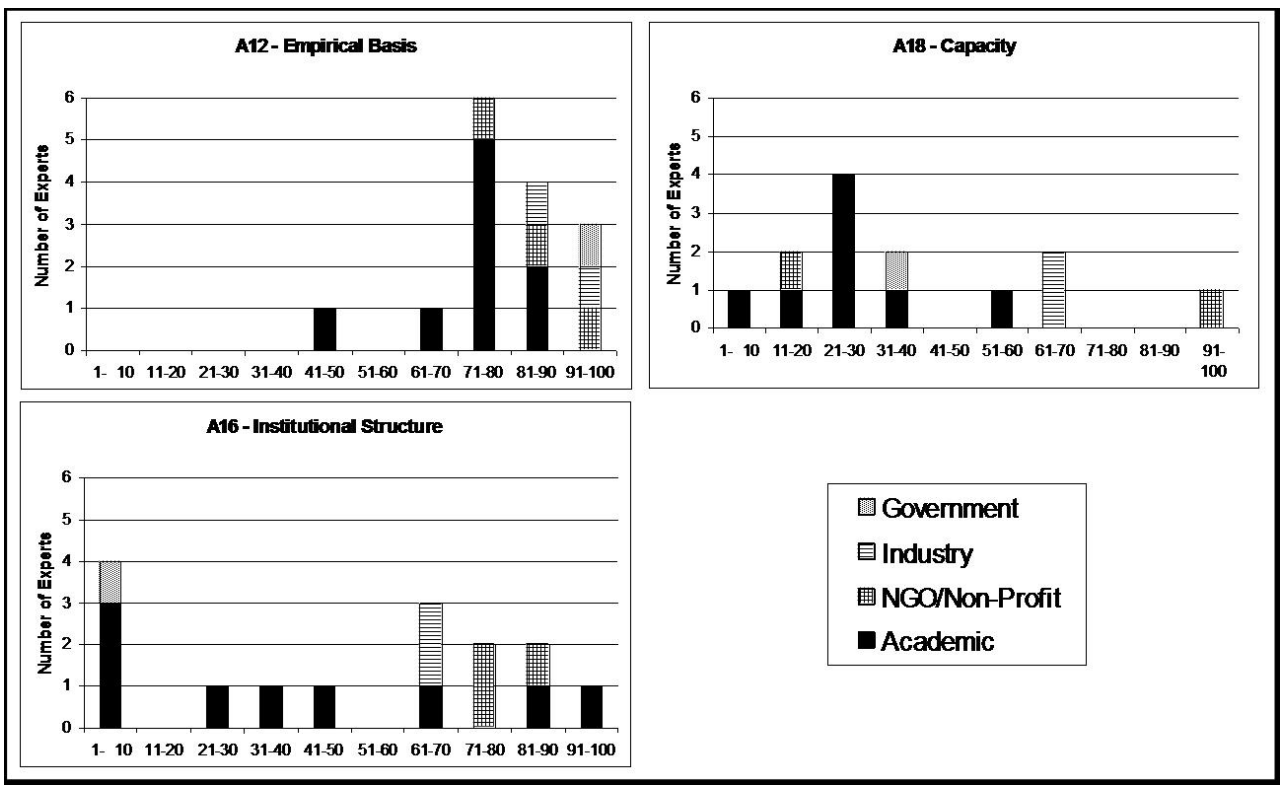
Criteria that demonstrated agreement by all three methods of evaluation were identified as high-agreement criteria. For drugs, there were eight such criteria: (1) clarity of technological subject matter (D2), where experts agreed that the technological subject matter was clear; (2) transparency (D5), where experts agreed that transparency was average – neither high, nor low; (3) data requirements and stringency (A9), where experts agreed that the data requirements and stringency for the drug oversight system were strong; (4) empirical basis (A12), where experts agreed that the oversight system had a strong empirical basis; (5) public confidence (O24), where experts agreed that the system had engendered a moderate level of public confidence (neither high nor low); (6) research and innovation (O25), where experts agreed that the oversight system did not have a negative or positive effect on future research and innovation; (7) health and safety (O26), where experts agreed that the oversight system had a positive effect on health and safety; and (8) environmental impacts (O28), where experts agreed that the oversight system had neither a negative or positive impact on the environment.

Criteria for drugs with low expert agreement may represent issues that are still under debate in the literature. There was low agreement for institutional

Figure 7

Examples of Histograms with Varying Levels of Qualitative Agreement

"High" is top left; "medium" is top right, and "low" is bottom left.



structure (A16), flexibility (A17), public input (A19), and conflict of interest (A21).

For devices, we found high expert agreement for treatment of intellectual property (A15), where experts agree that the oversight system was neither rigid nor entirely flexible to deal with unique issues; research and innovation (O25), where experts agreed that the oversight system had a slightly negative impact on research and innovation; and environmental impacts (O28), where experts agreed that the oversight system had neither a negative or positive effect on environmental impacts. There was low agreement for several criteria: clarity of technological subject matter (D2), empirical basis (D7), legal grounding (A8), institutional structure (A16), transparency (A20), conflict of interest (A21), informed consent (A22), and extent of change (E23). As with the three criteria of low expert agreement for drugs, this indicates that experts disagreed on whether these criteria were a strength or weakness of the device oversight system.

INFLUENCE DIAGRAMS

We use influence diagrams to show relationships between criteria that have emerged from analysis of our expert data. (See Figures 10 and 11.) Our criteria are

Figure 8

Levels of Agreement Summary for Drugs

Values that indicate high level of agreement are highlighted.

Comparison of Standard Deviations					Bins			Visual Qualitative Assessment
Criteria	Mean	Median	SD	N	n (1-30)	n (31-70)	n (71-100)	
D1	34	20	34	15	10	1	4	H
D2	71	80	22	14	1	4	9	H
D3	63	70	25	14	2	7	5	M
D4	68	73	23	14	2	5	7	M
D5	60	50	19	14	1	9	4	H
D6	48	50	25	13	4	7	2	L
D7	66	70	23	13	2	5	6	M
A8	65	70	24	15	2	7	6	M
A9	83	90	14	15	0	3	12	H
A10	57	60	23	15	2	10	3	M
A11	62	60	20	13	1	8	4	M
A12	83	80	12	15	0	2	13	H
A13	74	75	13	15	0	7	8	H
A14	68	70	22	14	1	7	6	M
A15	55	50	22	13	2	9	2	M
A16	53	65	34	15	5	5	5	L
A17	50	50	27	15	6	6	3	L
A18	42	40	25	15	6	8	1	M
A19	49	50	26	15	5	6	4	L
A20	48	50	24	15	4	9	2	L
A21	52	60	27	15	5	7	3	L
A22	67	78	24	14	2	4	8	M
E23	72	70	20	15	0	9	6	H
O24	49	50	14	15	3	11	1	H
O25	52	50	17	15	3	10	2	H
O26	73	80	19	15	1	5	9	H
O27	64	65	24	15	1	9	5	M
O28	48	50	17	12	3	8	1	H

divided into development, attribute, evolution, and outcome categories. The influence diagrams show arrows between pairs of criteria with a correlation coefficient of r^2=0.49 or higher. This numerical score can be interpreted as follows: if the correlation coefficient between two criteria is r^2=0.50, this means that 50% of the variation in one of the criteria is related to variation in the other. This indicates that a change in the expert rating of one criterion would likely indicate a similar change in the rating of the other criterion. In our study all of the correlations were positive, meaning that a change in one criterion corresponds to a change in the same direction in the other, i.e., the criteria either increase or decrease together. The p values were also measured for each correlation to determine the probability of getting a correlation coefficient as large as the given value due to random chance. For the statistically significant pairs of criteria listed, the p values were p<0.008 for devices and p<0.003 for drugs. The p value for each pair of correlated criteria is shown in Figure 12.

Note that an arrow on the influence diagram does not mean that the ratings for the two connected criteria are both high, low, or neutral. One of the pair may be rated high while the other is rated low. The influ-

Figure 9

Levels of Agreement Summary for Devices

Values that indicate high level of agreement are highlighted.

Comparison of Standard Deviations					Bins			Visual Qualitative Assessment
Criteria	Mean	Median	SD	N	n (1-30)	n (31-70)	n (71-100)	
D1	36	30	30	12	7	3	2	M
D2	53	50	23	12	3	5	4	L
D3	52	55	21	12	3	8	1	M
D4	61	65	23	12	2	5	5	L
D5	64	60	21	12	1	6	5	L
D6	38	40	24	12	6	5	1	L
D7	58	60	27	12	3	5	4	L
A8	55	70	27	13	3	5	5	L
A9	65	75	20	13	2	4	7	M
A10	45	50	22	13	3	9	1	M
A11	54	50	20	12	1	9	2	M
A12	67	70	20	13	1	7	5	H
A13	66	70	20	13	1	6	6	M
A14	62	70	24	13	2	7	4	M
A15	58	60	21	12	1	9	2	H
A16	53	50	32	13	5	5	3	L
A17	51	50	28	13	4	7	2	L
A18	41	30	24	13	7	5	1	M
A19	44	40	25	13	6	4	3	M
A20	48	50	26	13	5	5	3	L
A21	57	60	24	13	4	5	4	L
A22	58	60	24	13	3	4	6	L
E23	52	50	28	13	4	6	3	L
O24	43	40	18	13	5	7	1	M
O25	48	50	17	13	4	9	0	H
O26	64	70	22	13	2	5	6	L
O27	62	60	26	13	1	6	6	L
O28	50	50	12	11	1	10	0	H

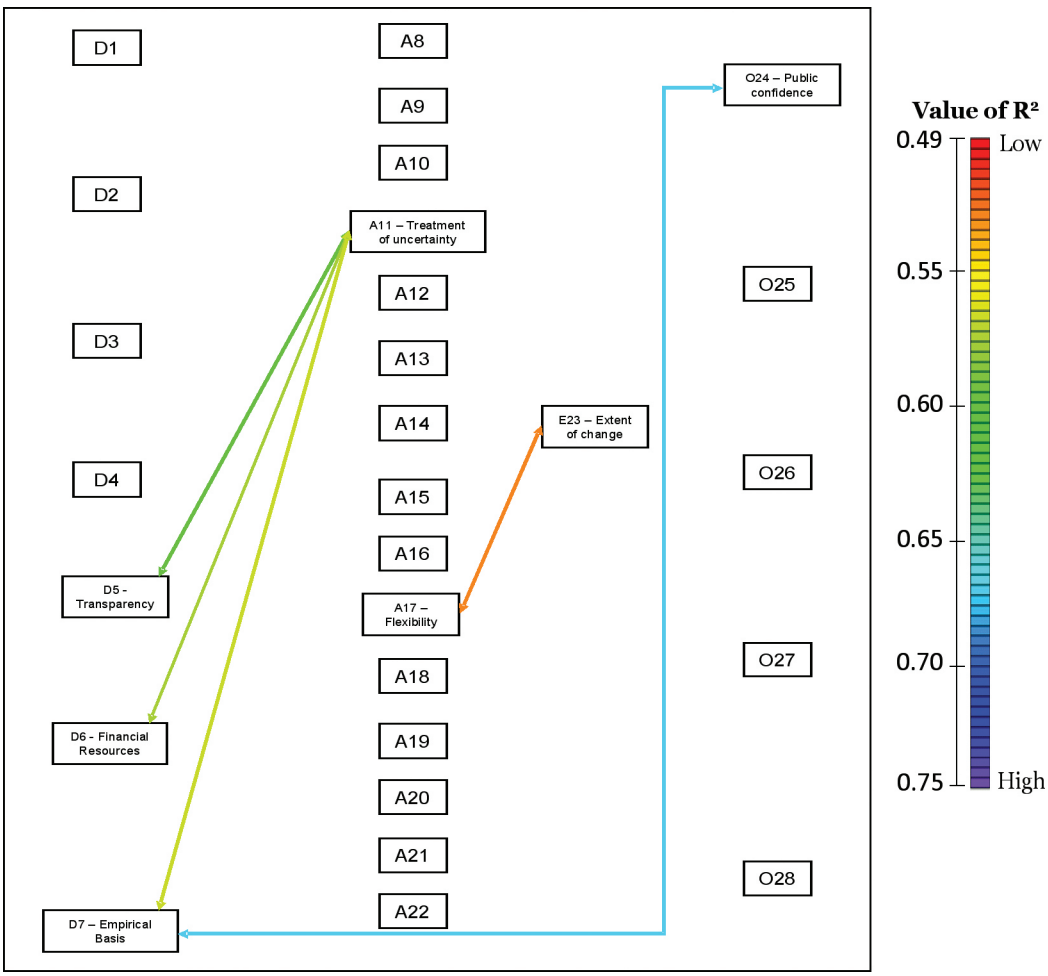
ence diagram provides information about the *change* in scores of correlated criteria. This analysis does not imply that a change in one criterion *causes* the change in the other, only that the perceptions of these particular experts travel in the same direction for both criteria simultaneously. Using the calculated r^2 value discussed above, we constructed influence diagrams for both drugs and devices. (See Figures 10 and 11.) The strength of each correlation is depicted by the color of the line. The drugs influence diagram shows only 5 significant correlations between pairs of criteria. (See list in Figure 12.) Three of these correlations are between three of the development criteria — D4 (public input), D5 (transparency), and D7 (empirical basis) — and A11 (treatment of uncertainty), suggesting that more extensive treatment of uncertainty can be achieved by creating a system with high transparency, sufficient financial resources, and a strong empirical basis. The only outcome criteria with a correlation were public confidence (O24) with empirical basis (D7). This was the most significant correlation for drugs, with an R2 value of 0.67. The relationship suggests that public confidence in the oversight system increases when the empirical basis for development of the system is strong. The final correlation is between the flexibility of the oversight system (A17) and the extent of change (E23). This relationship suggests that if the flexibility of a system increases, the extent of change in the system also increases.

The devices influence diagram is more complex, showing 22 significant correlations. (See Figure 13.) The strongest correlation is between financial resources (D6) and public input (A19). In contrast to drugs, all four of the outcome criteria have significant correlations (O24, O25, O26 and O27), as well as numerous criteria with multiple correlations, including financial resources (D6), treatment of uncertainty (A11), and distributional health impacts (O27). From

Figure 10

Influence Diagram for Drugs

The color of the line shows the strength of the correlation.



a statistical standpoint, this means that there are more pairs of criteria in which a change of expert opinion regarding one criterion of the pair is likely to reflect a similar change of opinion for the other criterion of the pair. The increased number of correlations for devices suggests that there are more aspects of the oversight system that are dependent on or linked to other aspects of the system.

The influence diagrams suggest that higher public confidence is linked to strong empirical basis, extensive post-market monitoring, and extensive treatment of uncertainty. Positive effects on health and safety were linked to greater transparency, sufficient financial resources, and stronger empirical basis.

C. Comparisons between Drugs and Devices

STATISTICAL ANALYSIS

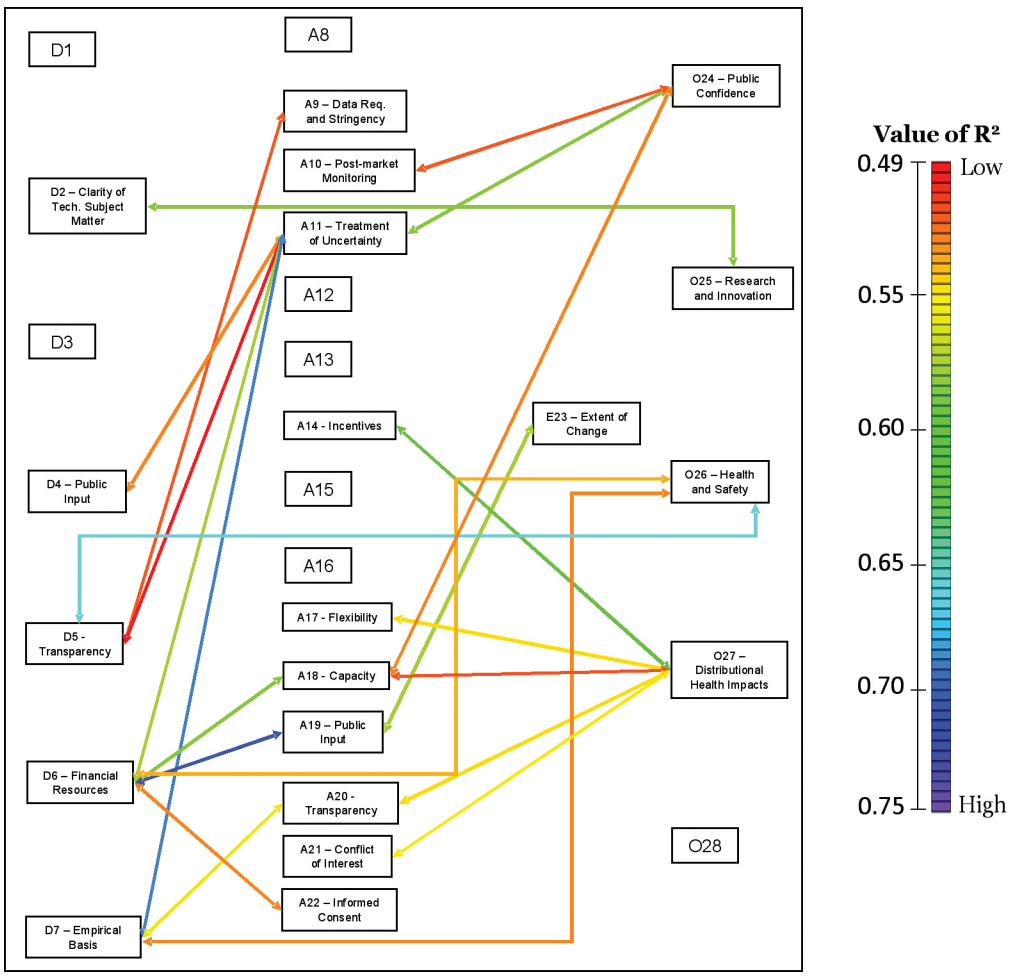
To identify similarities and differences between the drugs and devices data, we identified the criteria that were found to have high agreement or low agreement in both categories. There were two criteria on which there was high expert consensus for both drugs and devices: research and innovation (O25) and environmental impacts (O28). In both cases the experts agreed on a rating that was neither high nor low; instead, they felt that the oversight system neither stifled nor encouraged research and innovation and had neither positive nor negative impacts on the environment. This last point may result from the life cycle of the products, as drugs and devices are designed to be biomedical and not directly introduced into the environment. There were also two criteria on which there was low expert consensus for both drugs and devices: institutional structure (A16) and conflict of interest (A21).

Comparing data for drugs and devices revealed that for most criteria, the average for drugs was similar to that for devices. However, six criteria showed notably different means (more than 10 points apart): clar-

Figure 11

Influence Diagram for Devices

The color of the line shows the strength of the correlation.



ity (D2), legal grounding (D3), data requirements and stringency (A9), post-market monitoring (A10), empirical basis (A12), and extent of change (E23). In each of these cases the mean value was higher for drugs. For example, extent of change (E23) in drug oversight was seen as high, but extent of change in device oversight was seen as low. This suggests that our experts feel that the FDA is doing "better" (i.e., the criteria received higher scores on average) at regulating drugs than devices in these five areas. This finding could result from the relative newness of medical device regulation compared with that of drugs.

EXPERT AFFILIATIONS

Given the small sample size, we cannot draw any conclusions regarding the connection between experts' self-reported affiliation and their responses. However, we noticed a few general trends. We found that the two industry experts frequently answered very closely (differing by 29 points or less). In contrast, the academic experts varied more widely in their responses. This may be because the academics come from different disciplines and from backgrounds prior to entering academia. There were no obvious trends for the government or NGO/non-profit experts.

III. Using the Data to Address FDA Oversight of Drugs and Medical Devices

A. Identifying "Strengths" and "Weaknesses" of the Systems

The survey instruments were drafted to provide a range of responses from 0 to 100. At the far left of this range (0), we chose descriptors that were generally less favorable (e.g., weak, not at all, low), while those at the far right of the range (100) were described as generally favorable (e.g., strong, extensive, high). Thus, criteria responses generally array along a spectrum from less favorable to favorable, or from weakness to strength of the oversight system. Some criteria descriptions do not fit perfectly into this 0-100 framework, and we will discuss each criterion based on the description provided to the respondents.

The "strengths" and "weaknesses" of the oversight systems were identified based on the mean scores for each criterion. The numerical cut-offs differ between drugs and devices because the relative range of means varied between the two categories. Choosing different cutoffs for the two systems allowed us to identify relative strengths and weaknesses within each system. For drugs, means of equal to or above 70.0 were categorized as a strength, and means equal to or below 50.0 were categorized as a weakness. For devices, a strength was classified as having a mean equal to or above 60.0, and a weakness was classified as having a score of 45.0 or

Figure 12

Correlated Pairs of Criteria for Drugs and the Corresponding r^2 and p Values

Correlated Drug Criteria	r^2 value	p value
D5 & A11	0.61	0.001
D6 & A11	0.57	0.001
D7 & A11	0.56	0.001
D7 & O24	0.67	0.0002
A17 & E23	0.52	0.002

Figure 13

Correlated Pairs of Criteria for Devices and the Corresponding r^2 and p Values

Correlated Device Criteria	r^2 value	p value
D2 & O25	0.58	0.002
D4 & A11	0.52	0.005
D5 & A9	0.51	0.006
D5 & A11	0.49	0.007
D5 & O26	0.66	0.001
D6 & A11	0.57	0.003
D6 & A18	0.58	0.002
D6 & A19	0.71	0.0003
D6 & A22	0.51	0.006
D6 & O26	0.53	0.005
D7 & A11	0.69	0.0005
D7 & A20	0.55	0.004
D7 & O26	0.52	0.006
A10 & O24	0.51	0.006
A11 & O24	0.58	0.003
A14 & O27	0.60	0.002
A17 & O27	0.54	0.004
A18 & O24	0.52	0.006
A18 & O27	0.51	0.006
A19 & E23	0.57	0.003
A20 & O27	0.54	0.004
A21 & O27	0.52	0.005

below. (See Figure 14.) These results will frame the discussion in the remainder of the article, tying the expert elicitation results to the broader literature and case study. This will also contribute to the question of what makes a successful oversight system, using the terms "strength" and "weakness" in an extremely broad sense.

B. Discussion of Criteria

Having identified analyzed criteria above and identified oversight system "strengths" and "weaknesses" using the expert elicitation results, we now analyze criteria using existing literature, case law, and regulations to offer a historical, case studies approach. Below, we discuss criteria that seen by our experts across drugs and devices as either a system strength or weakness: D1, D6, A9, A12, A13, A18, A19, O24, and O26. We also discuss E23 as it relates to the evolution of the oversight systems.

D1: IMPETUS

This criterion was framed in terms of whether the systems were reactive (0) or proactive (100). This queries the historical context and driving forces behind the system of oversight or the reasons for developing the basic framework for the oversight system. Experts reported that impetus was reactive for both drugs and devices, which is in line with the literature spanning the one hundred plus years of drug oversight. Changes in regulation and stringency in oversight and enforcement have largely been brought about by specific events rather than concerted proactive action. This is understandable, in that it is often difficult to anticipate problems and the necessary adjustments to the system are clearest once a situation arises that threatens the public health.

The development of both drug and medical device oversight has been largely reactive, often driven by crisis. The Pure Food and Drugs Act of 1906 regarding adulteration and misbranding of food and drugs was promulgated as a result of concern over food safety. Amendments to the 1906 Act were introduced in 1938 as a result of over 100 U.S. deaths from "elixir of sulfanilamide" containing diethylene glycol. In 1962, the Kefauver-Harris Drug Amendments added efficacy as a requirement for approval after a finding that thalidomide contained in sleeping pills caused severe congenital abnormalities and birth defects. Safety and efficacy requirements (largely for drugs) were incorporated into medical device provisions with the Medical Device Amendments of 1976. The 1976 amendments were driven by a number of events, including a 1970 report released by the Cooper Commission (chaired by Theodore Cooper, M.D., Director of the National Heart and Lung Institute, now the National Heart, Lung and Blood Institute) that found over 10,000 injuries and 731 deaths attributed to medical devices. The amendments were also driven by market withdrawal of the Dalkon Shield intrauterine device due to reports of septic abortions and maternal deaths and

Figure 14

Strengths and Weaknesses for Drugs and Devices

Italicized entries were strengths or weaknesses in both drug and device oversight systems. The end of the range described in the survey instrument is in parenthesis following the criteria topic.

DRUGS		DEVICES	
Strength	**Weakness**	**Strength**	**Weakness**
D2: Clarity of technological subject matter (clear)	*D1: Impetus (reactive)*	D4: Public input (Significant)	*D1: Impetus (reactive)*
A9: Data requirements and stringency (strong)	*D6: Financial resources (not at all)*	D5: Transparency (High)	*D6: Financial resources (not at all)*
A12: Empirical basis (strong)	A17: Flexibility (low)	*A9: Data requirements and stringency (strong)*	A10: Post-market monitoring (little)
A13: Compliance and enforcement (strong)	*A18: Capacity (inadequate)*	*A12: Empirical basis (attribute)*	*A18: Capacity (inadequate)*
E23: Extent of change (extensive)	*A19: Public input (minimal)*	*A13: Compliance and enforcement (strong)*	*A19: Public input (minimal)*
O26: Health and safety (positive)	A20: Transparency (low)	A14: Incentives (many)	*O24: Public confidence (low)*
	O24: Public confidence (low)	O26: Health & safety (positive)	
	O28: Environmental impacts (negative)		

issues with the Shiley heart valve. Court cases in the 1960s upholding the FDA interpretation of a "drug" in order to require safety and efficacy information further advanced the discussion of the need for substantive requirements for medical devices.[73]

Subsequent amendments to the FDCA have also reflected a largely reactive response to high-profile recalls, litigation, and political pressures. The most recent amendments establish a more rigorous system of post-market monitoring and registration of clinical trials following several highly publicized drug and device recalls and lawsuits.

D6: Financial Resources

This criterion addressing the funding and resources devoted to the development of the oversight system ranged from insufficient (0) to sufficient (100). Our experts reported that financial resources were insufficient in the development of both the drug and the medical device systems.

The FDA's strength as an institution depends largely on resources determined by the presidential administration and Congress. A key factor in the capacity of the FDA to address health and safety questions is the resources available to it, including financial, personnel, and expertise. A major constraint on the FDA over the course of history has been its budget, the range of products it regulates, its ability to attract expert scientists, and its ability to balance multiple interests. A critical problem is that the FDA has limited resources that must stretch across all consumer products that the FDA regulates and all phases of these products — premarket, post-market, and enforcement.

A 9: Data Requirements and Stringency and A12: Empirical Basis

For purposes of discussion, we have merged the data requirements (A9) criterion with empirical basis (A12), as the two overlap and both were reported as strengths by our experts for both drugs and devices. The A9 category addressed the stringency of the system, including the extent to which empirical studies were submitted prior to market approval, release, or clinical trials, and whether there was adequate legal authority to require data. The response range provided was from weak (0) to strong (100). Our experts reported that data requirements and stringency were strong for both drugs and medical devices. "Empirical basis" addresses the amount and quality of evidence (scientific, risk, and benefit evidence) used for particular decisions. The response range provided was little (0) to extensive (100). Our experts reported that the empirical basis was extensive for both drugs and medical devices.

Drugs and medical devices regulated by the FDA are exposed to varying levels of scrutiny during evaluation for approval depending on their intended action, mode of action, and their level of risk. The scope and nature of data required by the FDA also vary according to the type of drug or medical device product, with new drugs and Class III medical devices requiring the most data upon submission of a product for review.

The FDA must determine for new drugs and Class III (high risk) devices how large of a risk is presented, the level of exposure that is safe, and the balance between the risk and the perceived magnitude of the benefits of the drug or medical device.[74] Generally, the onus is on the manufacture to prove safety and efficacy. The FDA does not make an explicit determination regarding the economic value or cost effectiveness of a new drug or high-risk (Class III) device, only its safety and efficacy based on a risk-benefit assessment of the submitted data and information.[75] Nor does the FDA compare competing products.[76]

There is ongoing difficulty in handling concepts of uncertainty and measures of "substantial evidence" in the approval process. Approval is at the discretion of reviewers who are often faced with industry, public, and administrative pressures to opt for a particular outcome. It is also important to recognize that "certainty" is a constantly evolving concept in the FDA, in that drug and device decisions are based on the current science and available data, which may change. Applicants must use evidence collected from well-designed and conducted experiments in order to reach a conclusion about the safety and efficacy of a drug or device. The FDA strives to assure that there is a minimal likelihood that the beneficial result in any given drug trial is a result of fraud, deceit, chance, or bias.[77] Measures of efficacy may also be problematic for a specific drug or device as they are context specific and patient specific. In addition, clinical trials may not always pose the proper clinical question or the trial may utilize an improper methodology.[78] These facts may only arise as data is collected as the trials evolve. Many side effects are unknown prior to approval and only post-market surveillance will be able to detect them.[79]

A constant struggle for the FDA is how best to balance the benefits of making a given health product or device available to the public with the risks posed. Once a product is approved, requirements for post-marketing monitoring depend on the type of product and range from voluntary to mandatory reporting requirements. The FDA also requires post-marketing notification of drug changes. The FDA depends heavily on industry and health care providers to report adverse events or other problems with marketed products. The most recent amendments to the FDCA

have focused on this as an important issue, increasing reporting requirements and tracking mechanisms. Safety issues can lead to product recalls.

Recent problems with implantable devices and drug recalls have increased debate about the adequacy of safety requirements. For example, the 2004 market withdrawal of Vioxx, a COX-2 inhibitor, was prompted by studies that emerged after approval indicating that COX-2 inhibitors might lead to heart attacks and strokes; one study reported that the drug doubled the risk in individuals taking it for over 18 months.[80] Merck & Co. ultimately voluntarily withdrew Vioxx from the market, but the incident raised questions about the FDA's initial approval of the drug, its post-market surveillance system, and the availability of risk studies generated by industry.[81]

Implantable cardioverter-defibrillator (ICD) controversies have highlighted the issue of post-market reporting and surveillance of medical devices. The 2005 death of Joshua Oukrop was traced to an ICD model manufactured by Guidant that had short-circuited while attempting to deliver high voltage therapy for arrhythmia. After Oukrop's death, physicians at the Minneapolis Heart Institute Foundation (MHIF) uncovered other similar reports from Guidant of short-circuiting.[82] Guidant had made manufacturing changes both in April and November 2002 after identifying electrical flaws,[83] yet continued to sell the older models susceptible to short circuiting. Guidant did not announce the modifications until two months after Oukrop's death.[84]

Drug safety information and adverse event reports, both mandatory and voluntary, are compiled, organized, and stored in a computerized database called the Adverse Event Reporting System (AERS).[85] It is used primarily by the FDA to facilitate post-marketing safety surveillance of products, but it also serves to disseminate information to the public. Quarterly files are accessible through AERS, containing raw data extracted from reports in the database. The files include information such as demographics, drug and reaction details, and patient outcomes.

The FDA's MedWatch program[86] provides tools to facilitate both mandatory and voluntary reporting, including forms and instructions for filing. It also gives updates about product safety and adverse events. Any consumer, patient, or medical professional who has experienced a serious adverse event or an issue with product quality or general product safety is encouraged to make a voluntary report through the MedWatch program. Drug manufacturers, packers, and distributors are required to report "serious and unexpected events" within 15 working days, or 5 days for deaths; for events deemed not "serious and unexpected," quarterly reporting is required.[87]

Post-market programs for safety of medical devices include recalls and Medical Device Reports (MDRs). Manufacturers must report adverse events to the FDA in MDRs, giving information on any deaths, serious injury, or known or reported malfunctions associated with a given device.[88] These reports are publicly accessible via the Manufacturer and User Facility Device Experience (MAUDE) database.[89]

A13: COMPLIANCE AND ENFORCEMENT

This criterion addressed whether programs and procedures are in place to ensure compliance with the oversight process, and when there is a lack of compliance, whether there are consequences and enforcement. This criterion was framed in terms of whether the system was weak (0) or strong (100). Our experts reported it as strong for both drugs and devices.

The FDA has a variety of enforcement tools, including warning letters to manufacturers that list violations and may require corrective action, civil actions (seizure, injunction, fines, and civil penalties), criminal penalties (fines and prison), and product recalls. There are also a variety of enforcement tools that are not specific to the FDA, including claims brought under the False Claims Act[90] and general criminal provisions such as mail fraud[91] and false statements.[92] There are additional legal actions that serve to compensate consumers for unsafe or faulty products on the market including product liability suits and other private civil actions.[93]

The FDA's approach to enforcement has varied over time as priorities, policies, budgets, and enforcement philosophies change. Particular industries, companies, or products may become targets because of product issues or media attention.[94] The FDA enforcement has thus ebbed and flowed based on changing signals from Congress, consumers, advocacy groups, and industry.[95] Enforcement agencies can use different approaches such as pursuing a wide number of cases involving particular conduct or imposing severe penalties on one or two entities as an object lesson to others. Enforcement activities are also strongly linked to the agency budget, with budget decreases reducing the capacity for enforcement.[96]

An area of increasing FDA scrutiny is "off-label" promotion, where a drug is promoted in a manner that exceeds its intended and approved use. The 1962 amendments to the FDCA gave the FDA explicit authority to regulate labeling and advertising of prescription drugs. The FDA's Division of Drug Marketing, Advertising, and Communications (a part of the Office of Medical Policy within CDER) is responsible

for ensuring that promotional information and materials regarding prescription drugs are not false or misleading. The FDA has a variety of enforcement tools in this area, including untitled letters requesting halt or correction of an advertisement, warning letters, health care provider letters that go directly to doctors, and formal legal action. Ultimately, off-label promotion violations can result in a number of federal actions involving the False Claims Act, the Lanham Act, product liability claims, and deceptive trade practice claims, as well as actions by the Securities Exchange Commission and liability to shareholders.

A18: CAPACITY

This criterion addressed the resources of the system, whether expertise, personnel, or financial, to appropriately handle decisions. This was framed in terms of inadequate (0) to adequate (100). Our experts reported that capacity was inadequate for both drugs and medical devices.

The FDA's mission and institutional structure are complex. As the federal regulatory agency responsible for the oversight of the majority of health and medical products in the United States, the FDA faces fundamental questions concerning its role in protecting the health and safety of the public while promoting innovation and development of useful and life-saving products, and its capacity to adapt over time. This criterion relates strongly to the previous criteria regarding data requirements, empirical basis, and compliance and enforcement mechanisms.

A19: PUBLIC INPUT

This criterion addresses the extent of opportunities for engaged stakeholders, including NGOs, trade associations, academics, industry, citizen groups, and other affected groups to provide input into specific decisions. This was framed in terms of minimal (0) to significant (100). Our experts reported that public input was minimal for both drugs and medical devices.

Public input can come into play at several stages with regard to drug and device oversight. The FDA takes into account various inputs when making decisions about products or trials. The use of experts and interested parties in the decision-making process is one way the FDA sets outs to accomplish this task.[97] The FDA regularly employs outside scientific experts as advisors on scientific and technological issues. Consumers, industry, and patient representative are also often present on advisory committees. The advisory committees typically consist of nine individuals: seven scientists, one industry representative, and one representative of consumer interests,[98] but only the seven scientists have voting rights.[99]

Each FDA center has specialized advisory committees assisting them in product review and decisions. The Center for Drug Evaluation and Research (CDER) currently has 16 advisory committees; the Center for Devices and Radiological Health (CDRH) has four, including a Medical Devices Advisory Committee made up of 18 panels covering medical specialty areas; and the Center for Biologics Evaluation and Research (CBER) has five.[100] The FDA also utilizes outside experts for special tasks, such as overseeing large product categories. For example, in 1966 the FDA contracted with the National Academy of Science and the National Research Council to assess the effectiveness of certain new drugs.[101] Scientists also assisted in classifying the 80+ therapeutic categories of OTC drugs following the 1962 amendments and the extensive tiered classification of medical devices in the 1970s and 1980s.

One major goal of public input is to provide transparency throughout the process of oversight. The issue of transparency is multifaceted, but deals generally with broad questions of the openness or concealment of scientific information and the extent of information available to interested parties throughout the oversight and regulatory process. Transparency involves active contributions and debate from any number of stakeholders including patients, health care providers, scientists and researchers, sponsors, policy makers, consumers, industry, non-profit organizations, and the general public.

The politicization of science and technology has been a topic at the heart of debate regarding the FDA and transparency over the last few decades, with discussion often hinging on the basis of policy formulation and the role of the "expert" in making decisions, the scientific value of trial data, and external pressures such as political, financial, or religious pressures. A 2006 Union of Concerned Scientists report investigated the current opinion of FDA scientists with respect to their role in the approval process. It revealed that the political pressures on scientists has led to interference with scientific determinations, a negative effect on public health, a negative effect on scientific candor, and immense pressures on agency scientists, including fear of retaliation for approval determinations.[102]

The administrative process of notice and comment rulemaking is one way the public is provided with information. Whenever the FDA proposes a new regulatory rule, there is a notice and comment period (usually 60 days) for the public to write in with comments. These comments are then reviewed, responded to, and posted with the final rule. The public can also offer testimony at public hearings and workshops. FDA also

makes extensive use of guidance documents to help inform stakeholders of current agency thinking on a variety of topics. Guidance documents are not binding on FDA or any stakeholder. There are two levels of administrative processes with varying degrees of public input involved in the creation of a guidance document depending on the substantive nature of the content.[103]

The public can also get information from the FDA through the Freedom of Information Act (FOIA). As a federal agency, the FDA is required to release information to citizens who request it, subject to some limitations.[104] Citizens' Petitions are another mechanism for public input regarding FDA regulations, policy, or scientific and safety issues. The FDA provides the right for a single citizen, group, or company to file a complaint or request with the FDA Commissioner.[105] Judicial review is available through the Administrative Procedure Act (APA), providing a right to citizens for federal district court review of a final agency decision.[106] The court may find the FDA action unlawful if it is contrary to law or "arbitrary and capricious," if there was an abuse of discretion, or if information was unreasonably withheld. The courts can enjoin FDA action. However, the courts traditionally show much deference to the FDA.

Scholars have described the struggle between progress in science promoted by publication of results, public discourse, and scientific sharing and the veil of secrecy marked by nondisclosure and withholding information from the public.[107] Some propose that in order to tackle the issue of transparency, release of information at each stage of drug and device evaluation and approval must be considered rather than allowing it to be kept secret as proprietary information.[108]

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E23: EXTENT OF CHANGE IN ATTRIBUTES

This criterion addressed the extent of change to the system over time. Change can indicate evolution of the system based on new information or in response to adverse events. This was framed in terms of no change at all (0) to extensive (100). Our experts reported that this was extensive for drugs.

Key changes in drug and medical device oversight have been driven by a public health problem, political pressure, new science, or societal changes. Major adjustments in drug oversight have often been triggered by serious adverse public health events such as those linked to sulfanilamide in the 1930s and thalidomide in the 1960s. Experts likely rated this as extensive for drugs due to the 100-year framework and shifts in oversight provisions resulting from advances in science and health care.

The original 1906 Act established manufacturing and labeling requirements for food and drugs, giving the FDA the authority to penalize any manufacturer for marketing a drug that was either adulterated or misbranded.[109] This was an enforcement statute and had no provisions for safety or efficacy approval prior to marketing of a drug. The legislation also placed the burden on the government to show proof that a product was contaminated, misbranded, or harmful, rather than on the manufacturer to show that it was not.

Unlike the century-long oversight of drugs, Congress first gave the FDA specific authority to oversee medical devices in 1938, with enactment of the Food, Drug, and Cosmetic Act (FDCA). However, this oversight was limited to provisions of adulteration and misbranding as laid out for drugs in the 1906 act. The 1938 act contained provisions for drug approval on the basis of safety, investigational new drugs (IND) approval process, factory inspections, and the remedy of court injunctions and seizures were initiated. The 1938 act was a vast improvement over the original act, in that it added safety data requirements, a requirement of toxicity testing, a burden on the manufacturer to show safety, requirements for registration by the manufacturer, inspections, and seizures as an enforcement mechanism. Medical devices were included in the 1938 FDCA because of the rise in marketing and

promotion of devices that were widely considered fraudulent by physicians.

The FDCA established provisions for drug approval on the basis of safety and initiated the investigational new drug (IND) approval process, mandating that manufacturers could not market the product without notifying the FDA and allowing it to assess safety based on data submitted by the new drug applicant. While the FDCA was the birth of the current system of premarket approval that applies now to practically all types of drugs, it was extremely limited in its regulation of medical devices. In early drafts of revisions that would become the FDCA, the definition of "drugs" was merely expanded to include "devices."[110] However, in subsequent iterations, devices were given an independent definition, and it was not clear whether new provisions for drugs applied to devices.[111]

The Kefauver-Harris Drug Amendments were a response to the finding that thalidomide sleeping pills caused severe congenital abnormalities and birth defects. The amendments added required FDA approval of NDAs and efficacy requirements for drugs, in addition to safety. New drugs developed and submitted to the FDA were also subject to retroactive evaluation for safety and efficacy through the Drug Efficacy Study Implementation (DESI).

In the years following the 1962 amendments, there was mounting concern over the increasingly complex medical devices entering the market for applications in coronary care, electronic equipment, and implantable devices.[112] The driving force behind calls for amendments pertaining to medical devices was the FDA's lack of authority to mandate safety of these new devices, instead limited to after-the-fact provisions allowing actions for adulteration or misbranding.

Between the 1962 amendments and the 1976 Medical Device Act, the FDA expanded the definition of "drug" to include a number of diagnostic products and instruments, highlighting the role of the FDA in shaping policy by approving specific products. [113] The courts were supportive of the FDA's actions in mandating safety data and approval for particular medical devices that they classified as new drugs. In the 1969 case of *United States v. An Article of Drug...Bacto-Unidisk*, the Supreme Court held that an antibiotic sensitivity disk that was external to the patient's body was nonetheless a "drug" subject to FDA approval because it contained antibiotics used to determine the patient's sensitivity level.[114] In a similar case, *AMP, Inc. v. Gardner*, the Second Circuit held that a suture product used to cut off blood flow through vessels during surgery should be broadly construed as a drug in light of the legislative history of FDCA.[115]

On May 28, 1976, the Medical Device Amendments (MDA) gave the FDA authority to regulate the safety and efficacy of medical devices. The amendments established a number of key provisions, including the following: a classification process for medical devices on the market; three separate levels of classes for medical devices that directly related to the level of regulatory control of the FDA; authority to create good manufacturing practice requirements (GMPs) and Quality Systems Regulation (QSR) requirements specifically for devices; a phasing-in of existing products into the new system; and post-market notification procedures.

More recent examples of changes in drug regulation include user fee legislation, safety-based drug recalls, and concerns about clinical trial methods and conflicts of interest.[116] User fees collected from industry in return for faster approval times is a recent development for drugs and devices. The Prescription Drug User Fee Act of 1992 (PDUFA) imposes fees on drug and biologic manufacturers for product applications and other stages in the approval process in exchange for quicker review by FDA (e.g., using funds to hire more reviewers). The PDUFA was reauthorized in 1997, 2002, and 2007. Similarly for devices, the Medical Device Used Fee & Modernization Act of 2002 (MDUFMA) became law in October of 2002, authorizing the FDA to charge a fee for medical device 510(k) reviews. It was reauthorized in 2007.

Changes in standards of evidence have been important over the years, including the number of studies required, the use of surrogate endpoints, and the monitoring and data collection. For example, the 1962 amendments to the FDCA established requirements for efficacy in addition to safety, setting out a requirement of "substantial evidence" derived from "adequate and well-controlled studies."[117] FDAMA in 1992 incorporated accelerated review into the "Fast Track" approval process allowing reliance on one clinical study; the FDA introduced a guidance document in 1998 that laid out circumstances under which they would rely on a single study in assessing a drug.[118] The FDA has also implemented provisions allowing use of surrogate endpoints, as with drugs to treat HIV infection and drugs intended for use with serious or life-threatening diseases when there is no available therapy.[119]

Recent amendments for devices include the Medical Device Amendments of 1992 (MDA),[120] the Food and Drug Administration Modernization Act of 1997 (FDAMA),[121] and the FDA Amendment Act of 2007 (FDAAA).[122] The MDA amended certain provisions regarding the reporting of adverse events, including defining certain terms and establishing a single

reporting standard for user facilities, manufacturers, and distributors. Mechanisms of post-market surveillance were improved by requiring that device-related serious injuries or deaths be reported by health care facilities, creation of tracking of high-risk devices, and giving authority to the FDA to require tracking for other devices at their discretion.[123] FDAMA provisions include accelerated review of devices and regulation of advertisement for unapproved uses of approved drugs and devices. FDAAA, enacted into law in 2007, reauthorized user fees established under PDUFA and MDUFMA and expanded the scope of clinical trial registration and post-market surveillance in response to growing concerns about public availability of trial information.

Implementation mechanisms and ultimate effects of FDAAA are unknown, but the legislation represents a strong step forward in increasing transparency in clinical trials and post-market monitoring of FDA-approved or cleared products and bolsters the FDA's enforcement authority. Commentators point out that FDAAA does not address issues relating to the design or conduct of clinical trials, nor does it address problems in regulatory agency decision-making.[124] Questions continue to arise as to public understanding and interpretation of clinical trial results, including how best to explain posted clinical trial information and what information materials should be developed to promote public understanding.[125]

FDAAA is likely to have a measurable effect on a number of criteria described in our project and in the legal and policy literature generally, including public input, empirical basis, data requirements, post-market monitoring, and conflicts of interest. For example, FDAAA includes numerous new provisions mandating or creating avenues for public input and mandatory public hearings and reports. The new legislation also strengthens the post-market surveillance system by adding to empirical basis requirements for continued marketing, expanding clinical trial databases, and adding surrogate endpoint provisions for pediatric provisions. FDAAA also provides new rules aimed at reducing the level of perceived conflicts of interest.

O24: PUBLIC CONFIDENCE

This criterion addresses the outcome of public confidence in the system, including views about product or trial safety and trust in the actors involved. This was framed as low (0) to high (100). Our experts collectively reported low public confidence for medical devices, although they did not agree that this was low for drugs.

Public confidence in the FDA has declined in recent years due to a number of high-profile product failures, recalls, and conflicts of interest. These events have contributed to increasing scrutiny of clinical trial information and disclosure mechanisms. A variety of public opinion polls (chiefly phone or online surveys) have been conducted over the last several years by organizations such as the *Wall Street Journal* and Harris Interactive,[126] Mellman Group and Public Opinion Strategies (commissioned by the Center for Congressional and Presidential Studies at American University and funded by Pfizer),[127] and the Union of Concerned Scientists.[128] The most recent *Wall Street Journal* and Harris Interactive study reported that U.S. adults assign negative ratings to the FDA for ensuring that new drugs enter the market quickly (60% negative ratings) and for effectively dealing with product recalls or withdrawals when safety issues arise (53% negative ratings).[129] Perceptions that the FDA is doing at least a "good" job to ensure the safety and efficacy of new prescription drugs has declined from past years, from 56% positive in 2004, to 45% positive in 2007, to 35% positive in early 2008.

Reports of increased scrutiny of internal conflicts of interest and concealment of expert disagreement with agency decisions are another factor influencing public confidence. Questions of investigator and sponsor conflicts of interest in clinical trials and financial conflicts of interest within the FDA and on advisory boards have been actively debated for years.[130] Critics urge that FDA advisory committees, intended to provide unbiased expert advice and input to the FDA on complex scientific and clinical issues regarding specific products, should have no members with financial ties to the company under review, such as owning stock in the company, or consulting for the maker of the drug or their competitor. Low recusal rates have been blamed for negatively affecting public confidence in the FDA; according to a study performed by the Public Citizen's Health Research Group, a financial conflict of interest was disclosed at 73% of the 221 FDA advisory committee meetings in 2002. Overall, 28% of advisory committee members had some sort of conflict of interest throughout the course of 2002, yet only 1% recused themselves from the committee meeting.[131] In response to concerns, 2007 FDA draft guidance requires advisory committee meetings to involve detailed disclosure of conflicts of interest. [132]

A major topic of public and political debate has been the need for FDA reform, highlighted by a series of reports by the Government Accountability Office, the National Academies of Science, and the Institute of Medicine. Many are eager to see results of FDAAA in areas rated most negatively by the public, including clinical trial and adverse event reporting, post-market

monitoring, conflicts of interest, and enforcement mechanisms.

026: HEALTH AND SAFETY IMPACTS

This criterion addresses health impacts as an outcome and whether oversight of the products or processes has led to impacts on global, national, or local health and safety. This was framed as negative (0) to positive (100). Our experts reported collectively that this was positive for drugs and devices.

The past decade has seen a number of conflicts within the FDA regarding allegations of the concealment of adverse events and drug side effects, leading many to criticize the FDA for valuing speed of approval over safety. The creation of user fees has also been criticized as threatening public safety because it creates a situation where a large portion of the FDA drug budget is directly funded by the pharmaceutical industry that it regulates.[133] Despite such criticism of FDA performance, our experts saw the health and safety outcomes as positive by our experts.

IV. Conclusion: Implications for Nanobiotechnology

The rising interest in nanomedicine, nanodrugs, and nanodevices, as well as the growing market impact of these nanotechnologies in health care and medicine, underscores the need for examining the potential application of existing regulatory systems to nanoproducts. A number of specific lessons emerge from our expert elicitation and broader examination of the literature that are relevant for nanotechnology applications in human drugs and medical devices.

The FDA has most often reacted to particular crises or pressure with regulation. If the FDA follows the oversight course of the past, regulation specific to nanotechnology will be driven by problems with some nano-product. This may be a particular drug or device, or it may be a product outside of the FDA's oversight scope, such as a children's toy or other consumer product that provokes regulatory action. In order to effectuate oversight, the FDA will need to determine in real time whether a new scheme specific to nanotechnology needs to be created and implemented or whether old frameworks can be adapted to incorporate the rapidly developing nanoproducts. While the 2007 Nano Task Force Report indicated there was no need to adjust existing frameworks at that time, emerging nanotechnology products may be challenging this conclusion; the report explicitly mentions the interface of drugs, devices, and biologics as one area of oversight that needs continuous evaluation as the science advances.

The FDA has various attributes regarding drug and device oversight that will be valuable as they develop nanotechnology oversight mechanisms or adjust existing mechanisms to encompass nanotechnology. Drug and medical device products undergo the most rigorous requirements of any consumer product, with data requirements and a spectrum of compliance and enforcement mechanisms. However, it is unclear whether these existing structures and the institutional structure of the FDA itself are suited to effectively oversee nanotechnology products. Questions exist as to whether there is adequate capacity to extend into this rapidly progressing area. There is also a broad issue of public input and whether the FDA operates with transparency and representation of relevant stakeholders in the oversight process and day-to-day decision-making.

One limiting factor for the FDA is the lack of financial resources. While the FDA has one of the largest budgets of any federal agency, their responsibilities are vast. Another hurdle will be that the FDA needs a clear regulatory definition of "nano" in place to oversee products through clinical trials, approval, and post-market surveillance. The century-old definitional frameworks for classifying a product as a drug, device, or biologic may be ill equipped to handle the convergence of properties at the nanoscale. Highly integrated nanotechnology products will pose a challenge to existing regulatory frameworks in the future because of integration of multiple modes of action in a novel manner. As written, the FDCA may not sufficiently distinguish products at the nanoscale. Rapidly developing applications in nanomedicine using mechanical, chemical, electrical, and optical properties at the nanoscale will likely add another layer to the classification challenge for the Office of Combination Products (OCP). Questions include whether this requires a distinct regulatory definition for nanotechnology for drug and medical device products; how this definition will vary from applications in other technical fields regulated by other federal agencies; and specifically whether distinctions between "chemical" and "mechanical" action need to be reassessed at the nanoscale.

Various other questions regarding the empirical basis of submissions, specific data requirements, and compliance procedures include whether the FDA should rely on the manufacturer to determine whether medical products are nano-products and report that in the submission process, whether guidance should be developed to aid manufacturers in this process, what should the manufacturer or physicians be required to report back to the FDA for nano-products, and whether there should be elevated reporting and post-market monitoring requirements for nano.

Questions of capacity include whether the institutional structure of the FDA supports additional, pos-

sibly distinct, oversight mechanisms for nanoproducts and whether the organization of the FDA into CDER, CBER, CDRH, and OCP is sufficient for drug and medical device nano-products. Further, what role should the public play in this process, and what is necessary to ensure transparency in the process? In this sense, transparency extends beyond the development of oversight for nanotechnology into questions of labeling and marketing, including when companies should be permitted, required, or prohibited from labeling their product as "nano."

In order to address these questions, additional scientific studies of toxicology and biological, chemical, mechanical, and optical features of nanotechnology in drugs and medical devices are warranted. Does reformulation of an existing drug into a nano-formulation change how the drug should be regulated? As mentioned before, the FDA is currently regulating nano-formulations in the same manner as larger versions of the drug. Are nanodrugs ever truly "therapeutic equivalents," or should they go through the entire new drug approval process to ensure safety and efficacy of the nano-formulation? Should manufacturers be permitted to seek approval for cancer nanodrugs through the accelerated approval process, or should the FDA require more testing before the product is marketed, due to the unknown risks?

As public confidence in the FDA has waned over the last several years, efforts should be made to tackle emerging questions about nanotechnology oversight, involving diverse stakeholders in the dialogue. While experts ranked health and safety outcomes as generally favorable as a result of oversight mechanisms in place for drugs and medical devices, nanotechnology may pose significant challenges to the FDA's current framework in the years to come.

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42. The medical device provisions allow manufacturers to file an Investigational Device Exemption (IDE) to clinically test experimental devices in order to acquire safety and performance data. This is similar to the IND process, except that approval by a local IRB is typically sufficient unless the process of review by the committee is found to be inadequate. 21 U.S.C. § 360(j)(g)(3)(A)(ii)(II) (2009). The FDA divides investigational devices into two categories: those posing "significant risk" with requirements similar to new drugs and those that do not pose significant risk where IRB approval and satisfaction of a number of other requirements achieves the IDE status without the rigorous application process. 21 C.F.R. § 812.2(b) (2009).
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