Navigating the U.S. Food and Drug Administration's Regulatory Science Initiative: An Imperative for Stem Cell Research and Regenerative Medicine Advocates

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“Regulatory science ... informs ... whole new ways of thinking about the potential of science.”

We're making huge investments in exciting biomedical research. But if those investments and discoveries aren't married to investments in regulatory science that allow us to understand what products are safe and effective and ready for widespread use, I don't think we can fully realize those investments.... I'd like to see us...working with the Science Board and a range of scientific organizations, professional research universities, industry scientists, and others. I'd like to develop a road map for strengthening *regulatory science* for the FDA and public health.

—U.S. FDA commissioner Margaret Hamburg, *personal interview, August 14, 2009* [1].

The [FDA] is a science-based agency responsible for regulating 80 percent of Americans' consumable goods and a quarter of the U.S. economy. It is imperative that every one of FDA's regulatory decisions be based on the best scientific evidence. Unfortunately, this has not always been possible due to several factors, including—but not limited to—inadequate human capital, leadership support, and funding. Above all, a weakening science base at the agency has threatened its ability to support its core regulatory functions and decisions. FDA needs to resolve *this gap between scientific and regulatory decision making* to ensure continuity of its duties in an environment of heightened public scrutiny on drug safety and rapid scientific advancements.

—Gail H. Cassell, *Co-Chair, Forum on Drug Discovery, Development, and Translation, Workshop Summary, U.S. Institute of Medicine, February 26, 2010* [2].

INTRODUCTION

On February 24, 2010, two days before the U.S. Institute of Medicine (IOM) workshop referenced in the second of the two above quotes, FDA, in collaboration with the National Institutes of Health, launched its *Advancing Regulatory Science* initiative (ARSI)—the program envisioned in Commissioner Hamburg's August 2009 re-

marks in the first of the two above quotes [101]. Eight months later, speaking at the National Press Club, Commissioner Hamburg presented the case for a \$25 million budget request for ARSI, and FDA simultaneously released a white paper describing regulatory science achievements already accomplished [102]. The first in this list was the development 6 years earlier of a method based on gene biomarkers for assessing the “stemness” of the cells com-

prising treatments derived from certain stem cell lines. Demonstrating the absence from such treatments of undifferentiated stem cells could potentially mitigate the risk of adverse side effects [3]. That this achievement was the first to be highlighted by the FDA to exemplify the value of regulatory science underscores an imperative for advocates of stem cell-derived regenerative medicine: they must become adept navigators of regulatory science.

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The move to science-based drug regulation

Regulatory science, as applied to medical products [the term used here to include drugs, biologics, devices, and cellular, tissue, and gene-based therapies (CTGTs)], is not a new concept. In a series of statutes passed in 1860, 1872, and 1875, the English Parliament replaced *six centuries* of food and beverage antiadulteration “assizes” dating back to decrees from King John—the monarch who signed the *Magna Carta*.¹ In these 19th-century statutes, Parliament moved to adopt analytical chemistry described in 1820 by Friedrich Accum in his *Treatise on Adulteration of Food and Culinary Poisons* [4].

The English statutes from the second half of the 19th century served as models for the U.S. Pure Food and Drug Act of 1906 (which sought to prevent adulterated and misbranded food from being introduced into interstate commerce in the United States) and its replacement, the U.S. Food, Drug and Cosmetic Act of 1938 (which added premarket notification from drug manufacturers to federal regulators to protect against unsafe products being introduced into interstate commerce in the United States).² In 1962, the Kefauver–

¹The assizes were designed to prevent adulteration of bread, ale, and other foods, with determinations as to whether a product was adulterated being based on the human senses of sight, smell, and taste. The assizes also served as the basis of English colonial law in America.

²Accum's analytical chemistry approach was championed in the United States by Dr. Harvey W. Wiley, a chemist and medical doctor who served as the chief chemist in the Division of Chemistry in the U.S. Department of Agriculture for 29 years, from 1883 to 1912. Reflecting Dr. Wiley's devotion to the need for a federal food and drug act, the Pure Food and Drug Act of 1906 is also called the “Wiley Act.” The initial focus of the 1906 Act was adulteration and labeling of foods and drugs, with safety coming expressly into the picture in the 1938 Act. Safety had been a focal point for the U.S. Biologics Control Act of 1902, which established licensing procedures for manufacturers of vaccines, antitoxins, and other biologically derived substances.

Harris Amendments to the 1938 Act—often described as Congress's reaction to the thalidomide tragedy of that time—switched from a premarket notification regime to a premarket approval regime and directed the FDA to add substantial evidence of efficacy as a requirement for approval of applications to introduce into interstate commerce new medicines. In response to this directive, the FDA developed a three-phase approach to clinical trials that has become the so-called gold standard for human clinical trials of new medical products. While used by industry and regulators around the world, this standard has come under increasing pressure for taking too much time and expense.³

Taken together, the 1902, 1938, and 1962 U.S. statutes authorize and direct the FDA, as a matter of law, to pursue a regulatory regime imbued with science. Against this backdrop, the term “regulatory science” can be used to describe the application of science to regulatory decision making, but in a broader context, the term can also be used to describe the application of science to the design of regulatory decision-making processes. Although the term “regulatory science” does not seem to appear with any recurring frequency in the relevant literature much before the beginning of the 21st century, the ying and yang of regulatory science can be seen in a series of actions, presentations, and reports involving the FDA that began in the late 1980s.⁴

³See, for example, the transcript of the debate “The FDA's caution is hazardous to our health,” held on May 8, 2013, sponsored by Intelligence Squared U.S., with Dr. Scott Gottlieb and Peter Huber for the motion, and Dr. Jerry Avorn and Dr. David Challoner against the motion, moderated by John Donovan. (The audience was polled before and after the debate, with the following results—before: 24% FOR, 32% AGAINST, and 44% UNDECIDED; after: 53% FOR, 38% AGAINST, 9% UNDECIDED.)

⁴For example, the journal *Science* contains only three articles before 2000 that contain the term “regulatory science.” This compares to over 30 such articles in that journal from and after 2000.

The emergence of regulatory science

The dearth of references to “regulatory science” before 2000 may owe in large part to the fact that before that time, as one commentator noted, “the activities of science in government policy [were] poorly documented and difficult to understand.”⁵

At the 1991 annual meeting of the American Society for Clinical Pharmacology and Therapeutics, two representatives of FDA's Center for Drug Evaluation and Research (CDER) used the term “regulatory science” to describe what was then a 3-year-old program to expand and train CDER's review staff for new drug applications. Concentrating this expansion on physicians trained in clinical pharmacology and adopting a medical school model, CDER created an internal staff college to train physicians in clinical pharmacology and regulatory science.⁶

Twelve years later, at the April 9, 2003, meeting of the FDA's science board,

⁵Foote SB. (1991). Working with experts. *Science* 251:210–211. In this review of Professor Sheila Jasanoff's *The Fifth Branch: Science Advisers as Policymakers* (Harvard University Press, Cambridge, MA, 1990), Foote explains that Professor Jasanoff addresses the lack of information about the role of science in regulatory policymaking through a series of case studies, primarily focused on the Environmental Protection Agency from its creation in 1970 through the deregulatory era of the 1980s. Foote notes that Professor Jasanoff drew a continuum from the “technocratic view that scientists should play a greater role in policy formulation and the democratic view that the public should participate in these essentially political decisions to protect against abuse of authority by experts.” This debate has not subsided and, perhaps, never will.

⁶Nelson RC and CC Peck. PIII-2 clinical pharmacology training at Food and Drug Administration. American Society for Clinical Pharmacology and Therapeutics Abstracts of papers, Ninety-second Annual Meeting, San Antonio, Texas, March 13–15, 1991. (Robert C. Nelson, PhD, served as the Director, Office of Professional Development and Staff College at CDER; Carl C. Peck, MD/PhD, served as the head of CDER.)

then-FDA commissioner Mark B. McClellan opened the meeting by stating that it would focus on “some of the key ideas that are part of FDA’s new Strategic Action Plan in the context of working to lower the cost of developing new pharmaceuticals, new devices, and other new medical products” while “trying to make sure we are using the best science, the best biomedical science, *the best regulatory science*, even the best economic science, in fulfilling this mission as efficiently as possible” [emphasis is the author’s own].⁷ (The FDA science board serves as the advisory committee to the FDA commissioner. It is referenced by Commissioner Hamburg in her remarks on regulatory science quoted at the beginning of this article.)

Dr. McClellan’s tenure as FDA commissioner ended in February 2004, when his board certification in internal medicine, doctorate in economics, masters in public administration, and well-honed interpersonal skills qualified him to fill the vacancy that had just opened in the Office of the Administrator of the U.S. Centers for Medicare and Medicaid. After his departure from FDA, science at FDA did not move sufficiently fast in the direction he had envisioned in 2003. In December 2006, confronted by the erosion in FDA’s capacity and resources for practicing the science needed to support its mission, Dr. McClellan’s successor, Dr. Andrew von Eschenbach, requested the Science Board to “form a Subcommittee to assess whether science and technology at the FDA can support current and future regulatory needs.”

In November 2007, less than 2 years before Commissioner Hamburg’s interview excerpted above, the subcommittee issued a bleak report giving three major reasons for FDA’s inability to fulfill its mission: first, the FDA’s “scientific base has eroded and its scientific organizational structure is weak”; second, the FDA’s “scientific workforce does not have sufficient capac-

ity and capability”; and third, the FDA’s “information technology (IT) infrastructure is inadequate.”⁸

In explaining the reasons for its conclusions, the subcommittee made repeated references to inadequacies in FDA’s regulatory science resources to keep abreast of two important related dynamics: (A) increasingly available information on the human genome and its impact on health, and (B) continuing emergence of biology as an information science. In the subcommittee’s view, the confluence of these two trends called for a new strategy at the FDA based on “a systems approach to understanding health and disease.” Adopting this approach would require the FDA to undertake “shifts in the substrate of regulatory science,” the outcome of which would be “a cross-disciplinary environment where biology, medicine technology and computation/mathematics can be seamlessly integrated.” The goal of this integration would be an “impact on drug discovery and the prediction of drug efficacy and safety, the integration of individual genomic information with technological advances in quantitative, unbiased, and hypothesis-driven biomarkers of drug action...likely to hasten the progressive personalization of medicine.”

Defining regulatory science

With only one year left in the 2005–2008 U.S. presidential term, the torch lit by the science board subcommittee in its November 2007 report was left to be passed to the FDA commissioner in the next president’s administration. Upon receiving it, Dr. Hamburg combined forces with NIH, where Dr. Francis Collins, the newly appointed NIH director, was determined to make an impact on translating science into medicine. In the ensuing burgeoning of the term “regulatory science,” its meaning became a bit like the proverbial description of an elephant by multiple

observers surrounding it at its different anatomical features—a parable that, according to its entry in Wikipedia, “has crossed between many religious traditions and is part of Jain, Buddhist, Sufi, and Hindu lore.”

As a matter of first impression, and without specifying any particular field of regulation or science, the phrase regulatory science can have two simultaneously correct general definitions, with selection of one or the other depending on which of the two words in the phrase is being used as the adjective of the other:

- *Type R* (with “regulatory” as adjective): the science in one or more scientific disciplines used for regulating, according to a predetermined method, a given field of commerce, industry, or other human endeavor.
- *Type S* (with “science” as adjective): application of the scientific method to government regulation made manifest through scientifically designed experiments—either real or simulated—to determine best methods for regulating the relevant subject matter.

In the context of FDA, the Type R definition expands to yield: (A) the development of life science tools by both regulators and industry that can be used by (i) industry to develop novel products and (ii) regulators to assess the safety, efficacy, and quality of those novel products; and (B) the use of life science by regulators for making policies about the requirements for market authorization approvals and postmarket approval evaluations of safety and/or efficacy. The example of the biomarkers for stemness described above exemplifies both arms of this expanded definition.

The subcommittee’s 2007 report reflected both the Type R and Type S definitions of regulatory science, when it described the term broadly as a science-based decision-making process needed to fulfill the responsibilities of a public health agency. In so doing, the subcommittee noted that the “FDA must have the scientific staff and resources to undertake the regulatory

⁷Opening Remarks of Commissioner Mark B. (2003) McClellan, Minutes of FDA Science Board Advisory Committee Meeting held by the FDA.

⁸Subcommittee on Science and Technology of the FDA Science Board, FDA Science and Mission at Risk, November 2007.

research that will provide a basis to: (i) improve capacity for safety and efficacy evaluations and monitoring of candidate and licensed products, (ii) modernize current regulatory pathways, and (iii) develop new regulatory pathways where there are currently none.”⁹ In recommending that the FDA establish a director of extramural operations and training, the subcommittee noted that one of this director’s tasks would be to “lead staff and develop collaborations and relationships... *with science-based advocacy groups* and industry” [emphasis not in original]. Realizing that the term “regulatory science” had come to mean different things to different people, or at least different things to the same people at different times, and that the budget request for \$25 million for the ARSI program could be the subject of Congressional scrutiny, the Forum on Drug Discovery, Development, and Translation within the IOM convened the one-day workshop referenced in the second of the two quotes at the beginning of this article. An objective of the IOM workshop was to “establish a clear definition of regulatory science, and engage the public and the policy community in a discussion of its challenges and opportunities.”

In a chapter titled Defining Regulatory Science in the summary of the workshop, reference was made to the following definition submitted by Dr. Carl C. Peck, adjunct professor of Bioengineering and Therapeutics Sciences at UCSF and chairman of a medical products consulting firm—the same Dr. Peck who, with his colleague Dr. Robert C. Nelson, used the term “regulatory science” at the 1991 ASCPT annual meeting (as described above):

Regulatory science is a broad term concerning drug and other product regulations, regulatory standards, law and procedures across many disciplines. It is a systemized body of knowledge (practiced by the FDA and similar regulatory agencies world-wide) comprising public

protection-oriented medical product regulations, policy and decisions using scientific methods employing empirical and causal evidence utilized in the evaluation and approval of all the products that the FDA regulates.

In her definition presented to the workshop, Commissioner Hamburg used words very similar to those offered by Dr. Peck, but added express references to “efficacy, safety, and quality.”

[Regulatory] science that underlies the development and utilization of new tools, standards, and approaches for the assessment of medical product efficacy, safety, and quality, is the critical bridge between basic scientific research discoveries and new marketed medical products. Regulatory science comprises an array of disciplines and approaches. Regulatory science not only takes place in laboratories, but it also may involve clinical, epidemiological, and statistical tools and information-gathering systems.

In offering this definition, Commissioner Hamburg further noted: “Unlike work performed by specific sponsors, regulatory science is important for multiple products and stakeholders. The knowledge generated from such studies informs a whole class of potential products rather than a single product. It informs, in some instances, whole new ways of thinking about the potential of science.” In its August 2011 Strategic Plan for Regulatory Science, FDA offered a distilled version of Commissioner Hamburg’s definition presented at the IOM workshop¹⁰:

the science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of FDA-regulated products.

FDA’s strategic plan set forth eight “priority areas of regulatory science” that FDA would pursue “through management of scientific programs within FDA and engagement of collaborators and partners in industry, academia, and government.” These eight strategic priorities address “cross-cutting needs and opportunities extending across several product areas.” The eight priorities are summarized in the left-hand column in Table 1, with the second column providing for each of these one or more examples of the role filled by stem cell science and regenerative medicine.

The examples in Table 1 help illustrate why it is vital for patient advocates to understand (a) the role to be played by Stem Cell Science and Regenerative Medicine (SCS&RM) in each of FDA’s regulatory science strategic priorities (even the one centered on food supply) and (b) the role that FDA expects patient advocates to play in advancing regulatory science.

FDA states in its strategic plan that it “can collaborate with partners from a wide range of other organizations including, but not limited to, *patient advocacy groups*, professional societies, charitable foundations, industry members, trade organizations, and academic institutions” [emphasis is the author’s own]. Exemplifying this point, in a November 2012 report on the elements of regulatory science applicable to SCS&RM, Dr. Raj K. Puri, director, Office of Cellular, Tissue and Gene Therapies in the FDA’s Center for Biologics Evaluation and Research, speaks to FDA’s efforts at community outreach and references a round table with CIRM, JDRF, ARM, and others, and engagement with patient advocacy groups [103].

Establishing the CERSIs

In February 2013, the FDA issued a “request for information” in respect of its plan to establish Centers of Excellence in Regulatory Science and Innovation (CERSIs), and/or similar partnerships and relationships, to address regulatory science challenges and opportunities [104].

⁹Id., p. 14.

¹⁰FDA. Advancing Regulatory Science at FDA—A Strategic Plan, August 2011.

Table 1. Applying FDA's Advancing Regulatory Strategy to Stem Cell Science & Regenerative Medicine

<i>Regulatory science strategic area</i>	<i>Examples of relevance for stem cell-based regenerative medicine</i>
1. Modernize Toxicology to Enhance Product Safety	NIH NCATS grant: Morgridge Institute for Research at the University of Wisconsin–Madison, Human induced pluripotent stem cell and embryonic stem cell-based models for predictive neural toxicity and teratogenicity, Principal Investigator: James A. Thomson, VMD, PhD
2. Stimulate Innovation in Clinical Evaluations and Personalized Medicine to Improve Product Development and Patient Outcomes	NIH NCATS grant: Columbia University Health Sciences, New York City Modeling complex disease using induced pluripotent stem cell-derived skin constructs, principal investigator: Angela Christiano, PhD
3. Support New Approaches to Improve Product Manufacturing and Quality	Quality by Design in Stem Cell Transplantation: Rational translation from bench to bed, Wednesday, May 1, 2013; Faculty of Medicine, Butnar Building, Butnar Small Hall, The Hebrew University of Jerusalem, Ein Kerem, Jerusalem
4. Ensure FDA Readiness to Evaluate Innovative Emerging Technologies	Participation in public hearings of the FDA advisory committees on market authorization applications in respect of stem cell-based regenerative medicines
5. Harness Diverse Data through Information Sciences to Improve Health Outcomes	Application of the technology embodied in the Stem Cell Matrix, an innovative information system developed in the laboratory of Dr. Jeanne F. Loring at The Scripps Research Institute
6. Implement a New Prevention-Focused Food Safety System to Protect Public Health	The use of stem cell lines for food safety tests
7. Facilitate Development of Medical Countermeasures to Protect Against Threats to U.S. and Global Health and Security	U.S. Biomedical Advanced Research & Development Authority (BARDA): Medical Countermeasures to Mitigate and/or Treat Ionizing Radiation-Induced Cutaneous Injury: Project Bioshield (RC1) (FY 2008): University of California–Los Angeles, Principal Investigator: William McBride, PhD, Mesenchymal Stem Cells to Mitigate and Treat Cutaneous Injury Following Radiation Mechanisms, Diagnosis, and Treatment of Radiation Injury from a Nuclear Accident or Terrorist Attack (R01) (FY 2008–FY 2010): University of Pittsburgh, Principal Investigator: Tao Cheng, MD, Negative Effects of Irradiated Hosts on Transplanted Hematopoietic Stem Cells
8. Strengthen Social and Behavioral Science to Help Consumers and Professionals Make Informed Decisions about Regulated Product	References to FDA's efforts at community outreach in November 2012 report on the elements of regulatory science applicable to SCS&RM by Dr. Raj K. Puri, Director, Office of Cellular, Tissue and Gene Therapies in FDA's Center for Biologics Evaluation and Research.

The purpose of this RFI was “to solicit informal input from the broader public and private sectors, including industry, academia, federally funded research and development centers, government laboratories, physician and pharmacist societies,

patient-focused research foundations and advocacy groups, as well as other health care providers” [emphasis is the author’s own]. The response date for this notice was April 1, 2013. (Patient advocates need to note that response deadlines on re-

quests such as this are relatively short and; therefore, they need to keep their antennae well-tuned.)

Six weeks later, on May 15, 2013, the FDA published a funding opportunity

A Brief History of Regulatory Science: From Origins to Current Use

1906—U.S. Pure Food and Drug Act

1938—U.S. Food, Drug and Cosmetic Act

1962—Kefauver–Harris Amendments to 1938 Act

1991—Term “regulatory science” used at the FDA meeting

2003 and 2009—the FDA cites abiding by and strengthening regulatory science as integral to its mission

announcement for the CERSIs, seeking applications by July 9, 2013, from single institutions and consortia to operate one or more CERSIs in order “to foster an innovative and thematically coherent approach to advance the field of regulatory science (including laboratory, population, behavioral, and manufacturing sciences) and the Critical Path Initiative toward more effective and efficient product development and evaluation.” These applications were to undergo scientific merit review on August 16, 2013, and Advisory Council Review September 9–10, 2013, with the potential earliest start date of September 23, 2013.

In sum, the FDA’s ARSI represents a significant platform that will affect the trans-

lation of stem cell science into regenerative medicine as well as the development of stem cell-based technology that will have broad application to the development and regulation of other areas of medicine, public health, and national security. For patient advocates of SCS&RM it is vital that they become expert at navigating the contours of regulatory science.

Author disclosure statement

Mr. Jakimo’s practice of law at Sidley Austin LLP includes representation of companies engaged in life science and life science finance.

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