

Towards an Applied Science of Therapeutic Regulatory Decision-Making

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US Food and Drug Administration (FDA) Commissioner Margaret Hamburg, M.D. departed the agency at the end of March, 2015 to assume the role of Foreign Secretary of the Institute of Medicine (IOM). One of her legacies as FDA Commissioner is the formalization and incorporation of “Regulatory Science” as an Agency priority [1,2,3]. We recommend that the Hamburg/FDA vision of regulatory science be further developed as two formal sciences: 1. a component which is comprised mostly of basic sciences; and 2. an applied science component related to how science is translated into regulatory decision-making and action. Each area deserves its own literature, history, methods and outcomes. A proposed name for the applied science component is the “Science of Therapeutic Regulator Decision-Making”.

The FDA definition of regulatory science concentrates on scientific intelligence, being consistent with the Agency’s authorizing legislation. It does not include the social sciences, economics and other applied sociological considerations (drug use behaviors). Although there is no international consensus on the definition of regulatory science, many agencies in Europe, Asia and Australia do include pharmacoeconomics, and other social considerations in their definitions [4,5].

A fuller science of regulatory decision-making in therapeutic areas has not received sufficient and careful attention. As a result, some regulatory decisions appear arbitrary. Moreover, the FDA must grapple with regulating new therapeutic areas, such as biosimilars, genomic therapies, and donor mitochondrial DNA for in-vitro fertilization (IVF), genomics testing and next generation sequencing tests (NGS). These are areas where no historical science on long-term safety and effectiveness exists for making regulatory decisions [6]. The entire realm of “personalize medicine” now being framed as “precision medicine” may also require unique approaches.

The complexity, costs, and dangers of advancing pharmacotherapy and other therapeutic and technological approaches in modern society warrant a different regulatory direction to assess non-clinical implications of the therapy and must encompass all public health outcomes, as well as therapeutic effectiveness and improved safety surveillance. Manufacturers, clinicians, scientists and regulators recognize that assessment is required over the lifecycle of an approved therapy. Our understanding of disease mechanisms and the impact of therapeutic approaches on individuals and populations continually improves. Though regulatory agencies in the US and Europe have gained increased authority to ask for post marketing safety and efficacy studies, there are few, if any, systematic scientific studies of regulatory decisions. The FDA has commissioned studies of administrative issues, such as first cycle performance. Likewise within the PBM industry, revisits to therapeutic effectiveness and safety (along with costs) are being stepped up, but without federal oversight.

Regardless of whether the regulatory agency has a legal mandate to consider non-scientific factors, these non-scientific factors often affect how approved therapies are accepted by clinicians, patients, and the general community, and used in the real world (the nascent science of pharmacoepidemiology). Moreover, the off-label use of approved medications is accepted practice, and seemingly justified using scientific and non-scientific considerations. The use of drugs off-label is

so widely accepted that with documentation, the Centers for Medicare and Medicaid Services (CMS) will reimburse for the off-label use of many anti-cancer drugs [7].

Translating scientific certainty and uncertainty into regulatory action requires, and receives, serious attention. Because there is no clearly defined methodology for translating scientific certainty and uncertainty into regulatory action, the evidence-based quality and interpretation of the benefit/risks of a particular therapy is often unclear at the time a decision is needed.

In other regulatory areas, such as environmental protection, [8] point out that regulatory science typically includes laws, regulations, and judicial decisions that often consists of: 1) science and 2) non-scientific areas that are typically outside the purview of science. They also go to great length about how various scientific data can be generically classified according to the strength of the scientific evidence [8].

Frequent questions about regulatory decisions include: is the data adequate for approval, since 36.8% of new indications were approved on a single pivotal trial (2005-2012); how do approved entities e.g., Resoline and Vioxx, get withdrawn from the market as unsafe; was the FDA justified in acting slower than Canadian or European Agencies on labelling testosterone with cardiovascular warning and incretins as having risk for pancreatitis and pancreatic cancer? Regulatory issues also arise about vaccine safety and effectiveness, and food safety. At time of this editorial, news headlines in referred Canada banning BMPEA as a food supplement for safety concerns, while the FDA still concludes the evidence is not strong enough to declare it unsafe. Also, since 1993, all EU countries have banned rBGH use in dairy cattle, but the FDA does not. Another challenge are drugs approved for one indication, withdrawn for safety or efficacy reasons, and then successfully reintroduced on the market for other indications. Viagra (sildenafil citrate) and Thalidomide are two well-known so-called Lazarus drugs.

When the benefit/risk assessment of an approved therapy becomes an issue, the agency is making an active decision regardless of whether they take an action or decide that no immediate action is warranted. Clinicians and patients need to be informed about such rationale for the action, or non-action, to have the most accurate information in which to make their personal benefit/risk assessments. Clinicians and patients

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Received April 16, 2015; **Accepted** April 17, 2015; **Published** April 25, 2015

Citation: Edlavitch SA, Salmon WJ (2015) Towards an Applied Science of Therapeutic Regulatory Decision-Making. J Pharmacovigilance 3: e137. doi:[10.4172/2329-6887.1000e137](https://doi.org/10.4172/2329-6887.1000e137)

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cannot know the pros and cons of a therapy as well as the experts who developed the intervention and the regulators (and their advisors) responsible for approving--and continually monitoring the body of safety and effectiveness data. A transparent science-based process, which also incorporates social sciences, economics and other "softer" applied considerations, will address situations where societal and financial considerations might override or seriously impact regulatory decisions.

As a result of Commissioner Hamburg's influence, the FDA vision is that regulatory action comes from the development and application of scientific methods, tools, approaches, and other relevant processes derived from various disciplines used in regulatory and policy decisions.

The priority areas for FDA regulatory science are to: modernize toxicology to enhance product safety; stimulate innovation in clinical evaluations and personalized medicine to improve product development and patient outcomes; support new approaches to improve product manufacturing and quality; ensure FDA readiness to evaluate innovative emerging technologies; harness diverse data through information sciences to improve health outcomes; implement a new prevention-focused food safety system to protect public health; facilitate development of medical countermeasures to protect against threats to U.S. and global health and security; strengthen social and behavioral science to help consumers and professionals make informed decisions about regulated products

The FDA is committed to engage collaborators and partners in industry, academia and government. The FDA Mini-Sentinel Initiative and the Observational Medical Outcomes Partnership (OMOP) are two public/private partnerships which have improved scientific methods and will provide the FDA and the medical community access to data on over 170 million persons.

In October 2011, FDA awarded \$2 million to launch Centers of Excellence in Regulatory Science and Innovation (CERSI) to work closely with FDA on projects related to specific priority areas in FDA's Strategic Plan to improve public health. Centers were established at the University of Maryland [9], Georgetown University [10], University of California at San Francisco with Stanford University (UCSF-Stanford), and Johns Hopkins University. The FDA and State of Arkansas have also established a Virtual Center of Excellence For Regulatory Science. Likewise, in Europe, the Escher Project, conducted by Leufkens et al (2007-2012) evaluated the long-term economic impact of regulatory decisions regarding a large number of drugs and conditions. The Escher Project's methods and findings could be an important component of a new science of therapeutic regulatory decision-making.

Recommendations

The following recommendations are presented as steps towards establishing a formal science of therapeutic regulatory decision-making.

1. Incorporate the science of regulatory decision-making as a component of the teaching, research and service of existing funded collaborative programs, such as the CERSI Centers.
2. IOM, EMA, WHO and the US FDA should create a collaborative project to
 - a. Develop a consensus definition for the Science of Therapeutic regulatory decision-making
 - b. Accumulate and provide access to a literature of drug/vaccine/device regulatory decisions.

- i. What was the strength of the scientific evidence available when a decision was needed?
 - ii. Were non-scientific factors parts of the decision-making process? Legal, Political, Patient-driven, Practitioner, Societal
 - iii. What were the outcomes of the decision? Public health, Economic, Political
- c. Discriminate between decisions which, in retrospect, appear to have been good versus those less than ideal using effectiveness, safety, and broad public health outcome criteria.
 - d. Explore applying standardized decision-making approaches. There is a growing literature on medical decision-making and the relationship to mathematical game theory [1,2] which needs to be reviewed.
 - e. Enhance existing educational programs, most of which currently concentrate on regulatory affairs. Develop the content of new educational programs with Identification of funding to enhance existing regulatory science educational programs.
 - f. Coordinate with programs in other countries that are addressing similar issues. It may be informative to compare outcomes in regulatory environments where the agencies may formally consider social sciences to the more restrictive environment in the US, where the FDA does not have that legal mandate.

The outcomes of collaboration on such issues demand a rigorous definition of the science of therapeutic regulatory decision-making and its application to the cycles of therapeutic development, marketing approval, post marketing monitoring and modification of indications and safety. Several innovative approaches to drug approval and post marketing surveillance are being considered or implemented, including conducting large scale pre- and/or post-marketing simple clinical trials to address potential safety problems, adaptive licensing and requirements for additional post marketing studies. In a 2012 review article, Dr. Jane Woodcock of the FDA suggested that none of these improvements will adequately address many of the scientific uncertainties that have led to most clinical development failures [13].

Establishing the "Science of Therapeutic Regulatory Decision-Making" is integral to ensuring that regulators have the best information available to make quality decisions on the drugs, treatments and interventions they must consider. This Science will help to save lives, and if adapted properly, will lead to a future with improved regulation and better public health outcomes. Perhaps in her new role as Foreign Secretary of the IOM, Dr. Hamburg will encourage the appropriate US and international committees to consider these recommendations.

Acknowledgement

Thank you to Dean Patricia Byrns, Mr. Seth Edlavitch, and Mrs. Carol Edlavitch for their valuable editorial comments in preparing this manuscript.

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doi:10.4172/2329-6887.1000e137

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