REGULATORY SCIENCE

Unmet needs: Research helps regulators do their jobs

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A plethora of innovative new medical products along with the need to apply modern technologies to medical-product evaluation has spurred seminal opportunities in regulatory sciences. Here, we provide eight examples of regulatory science research for diverse products. Opportunities abound, particularly in data science and precision health.

Translational biomedical science has emerged as a critical research theme over the past decade and encompasses the spectrum of scientific activities from basic discovery to clinical trials to strategies for clinical implementation. Central to translational medicine is an understanding of the path that moves basic science discoveries toward improvements in clinical practice, which includes robust mechanisms for evaluating the safety and efficacy of potential new diagnostics and therapeutics—some of which are ultimately approved for human use. Under development are myriad new health care products derived from cutting-edge science, such as genomics-based diagnostics, interventional imaging techniques, combination devices with biological materials, and cell-based therapies, and regulators need to apply modern technological tools and make full use of scientific advances to evaluate the benefits and risks of generation medical products. "Regulatory science" refers to investigations that generate fundamental knowledge necessary for driving regulatory decision-making. Regulatory science is like all scientific research in its emphasis on hypothesis generation and experimentation, but it focuses on questions whose answers are of particular importance for regulatory decisions, including those related to food, veterinary products, drugs, diagnostics, devices, and medical software.

In the United States, the U.S. Food and Drug Administration (FDA) has long recognized the importance of regulatory science for its mission. A 2007 study of the FDA Science Board (*1*) pointed out several challenges facing the agency, which resulted from rapid scientific and technological advances, globalization, and an increase in the complexity of medical products and therapies, and emphasized the need to respond with a new scientific strategy. In 2010, FDA introduced the Advancing Regulatory Science Initiative and an associated strategic plan (*2*), which outlines a broad set of activities in research and education to meet the avalanche of scientific opportunities and challenges. Several foundations—including the Burroughs Wellcome Fund, the PhRMA Foundation, the Reagan-Udall Foundation, and the Critical Path Institute—have provided funding or developed programs specifically directed at research and training in regulatory sciences. FDA initiated a new program that provides funds to academic institutions for the building of Centers of Excellence in Regulatory Science and Innovation (CERSI) and has thus far made four awards, including three in the vicinity of FDA's White Oak campus (at Georgetown University, Johns Hopkins University, and the University of Maryland) and one on the West Coast that represents a collaboration between the University of California, San Francisco (UCSF), and Stanford University (*3*).

The CERSI program has as its mission to identify opportunities for academic, industry, and FDA scientists to collaborate on research that advances regulatory sciences. Critical to the selection of collaborative research projects is an understanding of the key unmet needs in regulatory science. Examples are provided in FDA's strategic plan (Table 1) and across its electronic web infrastructure within individual centers, such as the Center for Drug Evaluation and Research (CDER) (*4*), Center for Tobacco Products (CTP) (*5*), Center for Devices and

Table 1. Strategic areas of regulatory sciences research. Information in the table is from www.fda.gov/downloads/scienceresearch/specialtopics/regulatoryscience/ucm268225.pdf.

Strategic research area	Examples of research
Modernize toxicology	• Develop better preclinical models of human adverse events • Use and develop computational methods for predicting drug toxicities
Stimulate innovation in clinical evaluations and personalized medicine	• Develop a virtual physiological patient • Identify and qualify safety and efficacy biomarkers
Support new approaches to improve product manufacturing	• Enable development of improved manufacturing methods (for example, continuous manufacturing versus batch) • Develop and implement modern analytical methods for evaluating product quality (for example, nuclear magnetic resonance imaging)
Ensure FDA readiness to evaluate innovative emerging technologies	• Develop assessment tools for novel diagnostics and therapies • Enhance readiness for new applications of information technology
Harness diverse data through information sciences	• Enhance information technology infrastructure • Develop simulation models for product life cycles, risk assessment, and other regulatory sciences uses
Implement a new prevention-focused food safety system	• Improve information sharing internally and externally through improved IT systems • Develop methods for rapid detection of pathogens that contaminate foods
Facilitate development of medical countermeasures	• Develop, characterize, and qualify animal models for medical countermeasures • Develop high-throughput methods to detect threat agents
Strengthen research in social and behavioral sciences	• Develop methods for aggregating patient preference information with clinical data • Develop best practices for patient preference elicitation studies

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Radiological Health (CDRH) (*6*), and Center for Biologics Evaluation and Research (CBER) (*7*). Further, FDA's list of unmet needs in regulatory science is posted in the Federal Register and includes the development of predictive methods for drug safety (*8*), tools for the assessment of patient-reported outcomes (*9*), and new approaches to ensure the analytical and clinical validity of next-generation sequencing (NGS) tests (*10*). In addition, the UCSF-Stanford CERSI informally surveyed FDA scientists so as to create a working list of the unmet research needs that are amenable to contributions from academic scientists at UCSF and Stanford, in collaboration with the FDA.

Here, we present eight examples of unmet needs in regulatory sciences that are derived from the various sources described above. These examples are by no means intended to cover the entire spectrum of research needs. We begin with data science—which crosses various centers at FDA—and then provide examples from FDA's CDRH, CDER, and CBER. We also highlight emerging interactions between FDA and other federal agencies such as the National Institute of Standards and Technology (NIST), which is interested in establishing standards that are applicable to a variety of FDA-regulated products, including NGS.

ENHANCE POSTMARKET VIGILANCE

Data science is the use of advanced computational and statistical methods to extract knowledge from raw data and has permeated the entire biomedical research enterprise. FDA has identified several challenges in the collection, organization, integration, and analysis of data. In particular, several centers at FDA have recognized the opportunity to improve postmarketing vigilance and recognize safety and, perhaps, lack of efficacy signals more quickly. FDA's Sentinel Initiative (*11*) has created a confederation of health care records for more than 100 million Americans for postmarket monitoring of the safety of FDA-regulated medical products and can distribute queries to sites across the nation and receive answers that can then be combined meta-analytically. The Sentinel Initiative is complementary to a longstanding infrastructure for spontaneous reporting as a source of signals for marketed products. Indeed, the FDA Adverse Events Reporting System (FAERS) (*12*), Vaccine Adverse Event Reporting System (VAERS) (*13*), and Manufacturer and User Facility Device Experience (MAUDE) (*14*) receive thousands of reports each month.

The availability of these data creates an opportunity to use advanced data-mining and machine-learning technologies for evaluating the quality of reports (for example, choosing more reliable versus less reliable reports to prioritize in review), detecting latent signals in databases that might be signatures involving several coincident adverse events, and linking spontaneous reporting systems to the electronic health records (available through the Sentinel Initiative, for example) for the purpose of initial automatic triage of potential safety signals. In addition to opportunities for mining clinical data and adverse event reports, there are intriguing regulatory science opportunities for combining "-omics" measurements with these data in order to generate hypotheses about the molecular mechanisms of adverse events. Currently, reported adverse events often have unclear biological or pharmacological mechanisms. However, clinical adverse event reports might be connected to genomic variation via variations in key pharmacokinetic genes involved in drug metabolism and transport. Indeed, the integration of clinical data and spontaneous reports with genome sequence, gene expression data, and chemoinformatic analysis of drug binding to targets and off-targets is a critical element of regulatory science that depends heavily on the development of new tools for the analysis and modeling of biomedical data.

NGS REGULATORY ARCHITECTURE

Broad clinical adoption of NGS in health care depends on establishing a path to regulatory oversight. Clinical promise has been demonstrated with early applications in rare familial diseases (*15*), oncology (*16*, *17*), infectious diseases (*18*), and noninvasive prenatal genetic testing (*19*). WGS and whole-exome sequencing (WES, a sequence of the annotated coding regions of the genome) powered by NGS present both technical and clinical departures from established single-gene Sanger sequencing (*20*). The key challenge to regulatory oversight of NGS as an in vitro device (IVD) is the absence of systematic ways to develop, present, and report evidence of the performance of a test that measures and reports at the genome scale (thus implicitly reporting thousands or millions of genetic test results per individual). A recent white paper from FDA has identified the new challenge of regulating NGS: "[T]his technology allows broad and indication-blind testing and is capable of generating vast amounts of data, both of which present issues that traditional regulatory approaches are not well-suited to address" (*21*).

An alternative approach suggested in this same white paper is to develop and use methodological standards and curation to evaluate safety and efficacy: "Among the possibilities, a standards-based approach to analytical performance of NGS tests and the use of centralized curated databases containing up-to-date evidence to support clinical performance are under discussion." A standards-based approach is a plausible path to presenting evidence but needs to be responsive to the architecture of clinical NGS—an enterprise-scale, multistage process using diverse technologies, knowledge, and skills. At present, a comprehensive set of standards does not exist, either because it has not been developed or because knowledge gaps must be addressed before such standards can be developed.

A standards-based approach to establishing the safety and efficacy of NGS and other emerging "-omic" technologies has the critical potential to be enduring, technology-agnostic, and modular. Modularity enables components of a diagnostic pipeline to interoperate, bringing economies of scale, specialization, and raising of the quality bar through sharing and transparency (*22*). A sequential roadmap, from sample collection to interpretation of data and patient reporting, is illustrated in Fig. 1. The NGS diagnostic enterprise is described in Table 2, from clinical sample through diagnosis, reporting, and data archival. Stratified by current technical and practitioner limitations, Table 2 suggests evidence appropriate for validation, the standards or practices that could be used to establish that evidence, and the critical stakeholders that can be convened to identify existing standards, create new standards, or establish the research agenda that would underlie the needed standards.

Knowledge gaps in each of the stratified boundaries (Table 2) represent opportunities for translational research. For example, new technology clearly is needed for the sequencing of regions of the genome that contain structural elements that make sequencing difficult. Functional annotation of both noncoding and coding polymorphisms is needed to identify functional variants linked to disease or to drug response that then can be used in the diagnosis of disease or the selection of medication and dose. Regulating the complex multistage ap-

proval process for NGS-based disease diagnosis and treatment calls for a deep understanding of the mechanistic basis for the relationships between genome variation and risk for disease or nonresponse or adverse response to medications. The genetic variants can be assembled in many permutations; the number of distinct clinical results from a genome-based test is unprecedented (and include incidental findings), and the technologies are evolving, even in the fundamental physics of these measurements. Scientific research opportunities and collaborations between FDA, NIST, and academic and industrial scientists are available and clearly needed to support a new standards-based regulatory framework for NGS.

SOCIAL AND BEHAVIORAL SCIENCES

The balance between the risks and benefits drives decisions about the approval of medical products. For example, high toxicity might be acceptable for drugs used in the treatment of life-threatening conditions such as pancreatic cancer but not acceptable for drugs used chronically to prevent disease (for example, statins used to reduce serum cholesterol levels). Measuring of clinical effectiveness, clinical harms, and the relative importance of various treatment outcomes remains challenging. In addition, quantifying the willingness to accept greater risks in exchange for treatment benefits involves subjective judgments of multiple decision-makers, including patients, health care providers, and regulators. The evaluation of risks and benefits might be further complicated by the lack of a consensus among these decision-makers.

In regulatory decisions, there has been a substantial increase in the consideration of patient preferences and perspectives about the benefits and risks of medical treatments. Indeed, regulatory science research currently focuses on the development of (i) best practices for preference-elicitation studies and benefit-risk communication and (ii) appropriate methodologies for aggregating patient preferences with clinical data.

In 2012, the FDA Center for Devices and Radiological Health (CDRH) released a guidance document encouraging sponsors to include patient perspectives in submissions to the agency (*23*). To provide a quantitative framework for incorporating patient preferences, CDRH reviewers developed a proof-of-concept tool based on quantitative measures of the importance of safety, efficacy, and other attributes of weight-loss devices for obese patients (*24*). The study collected preferences of more than 600 obese respondents and used the data to inform regulatory assessment and approval of the EnteroMedics Maestro Rechargeable System for weight loss. After publication of the proof-of-concept study, CDRH released a draft guidance on the inclusion of patient preference information that can be used by FDA in decision-making for the acceptance of premarketing approval (PMA) applications, humanitarian device exemption (HDE) applications, and de novo requests (*23*). Further, patient perspectives on product labels are increasingly being factored into regulatory decisions. For example, the proposed changes to the nutrition facts label from FDA's Center for Food Safety and Applied Nutrition were based in part on consumer preferences (*25*–*27*).

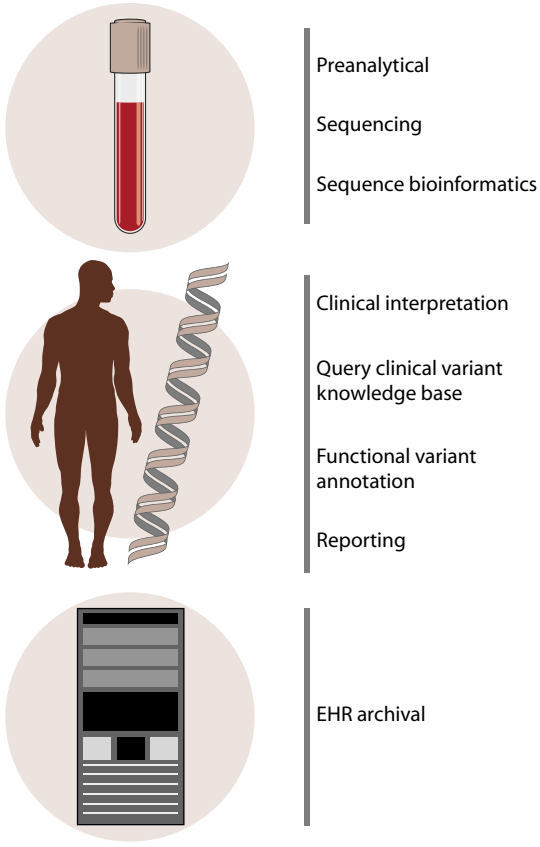

Fig. 1. From laboratory to patient to the cloud. Shown is a test architecture for whole-genome sequencing. The flow chart represents a proposed sequential roadmap for using DNA sequencing data in a clinical setting, from sample collection to the determination of genome sequence to the interpretation of data and patient reporting. Regulation of diagnostic tests requires the development of standards and methods for the use of next-generation sequence data in clinical decision-making.

SPINAL DEVICES

FDA evaluates hundreds of premarket submissions for spinal implants annually in order to ensure their reliability and safety before implantation. The majority of these devices—which, in general, stabilize the spine to relieve nerve root compression and associated pain—are classified as Class II devices regulated through the 510(k) pathway (www.fda.gov/RegulatoryInformation/Guidances/ucm072459.htm). The premarket laboratory assessment of the mechanical properties of such devices is performed in accordance with standards of the American Society for Testing and Materials (ASTM) F1717, which uses a vertebrectomy model based on polyethylene blocks. Clinical studies documenting the performance of many of these devices have been published (*28*) and can be used in conjunction with new research on the building of computational models that simulate in vivo device performance and assess the correlation with laboratory performance measurements. Data science techniques can then be used to identify the appropriate performance parameters for specific device types and correlate their in vitro with their in vivo performance. The application of transparent evidence-based regulatory processes in the approval of spinal devices is critical to ensuring that safe and effective devices are marketed and used, but successful approaches will also be applicable to the approval of other medical products, including implantable diagnostic devices.

NANOMATERIALS

Consumer products regulated by FDA might now contain nanomaterials—particles whose size is in the nanometer range and thus much smaller than a cell—and their safety is currently evaluated on a case-by-case, product-specific basis. Rapid advances in nanotechnology have increased the number of nanoproducts used in medical products, such as micellular nanoparticle emulsions of hormones, and this surge has raised safety concerns for both the environment and human health (*29*). We urgently need methods

Table 2. NGS: Diagnostic enterprise from clinical sample through diagnosis, reporting, and data archival. Shown is (i) suggested evidence appropriate for the development of validation standards, which could then be used to establish that evidence, and (ii) critical stakeholders who can be convened to identify existing standards, create new standards, or establish the research agenda that would underpin the needed standards. VCF, variant call format; SOP, standard operating procedures; SDOs, study delivery operations specialists; HHS, health and human services.

Phase	Evidence needed	Standards and evidence-developing practices (examples)	Stakeholders for standards development	Knowledge gaps (examples)
Preanalytical: from tissue to DNA	• Representative sampling • Accurate (unbiased) extraction • Integrity of DNA	• Documentary standard to establish SOPs for sampling • Reference samples and interlaboratory studies to evaluate extraction and DNA integrity	• Clinical laboratories • Professional societies • Clinical SDOs	• Artifacts associated with extraction from archival tissue samples
Sequencing: from DNA to raw sequence data "Wet bench"	• Accurate (unbiased) sequencing • Fit-for-purpose characteristics	• Well-characterized genomic DNA reference materials • Documentary standard describing sequencing characteristics appropriate for different clinical indications	• Standards laboratories • Clinical laboratories • Sequencing technology developers • Academic laboratories developing methods • Genome centers	• Sequencing of "difficult" regions of the genome • Platform artifacts • High-quality benchmark genomes • Performance expectations (sensitivity, specificity thresholds)
Sequence bioinformatics: from raw sequence data to VCF "Dry bench"	• Unbiased processing of sequence data (mapping and assembly) • Accurate variant calling • Accurate and unambiguous variant representation • Interoperability of data representation	• Documentary standards describing protocols to critically evaluate processes, coupled to knowledge of technical platform idiosyncrasies • Data representation standards • Reference data, implementation: benchmark VCF files • Reference software to evaluate VCF files	• Standards laboratories • Clinical laboratories • Sequencing technology developers • Academic laboratories developing methods • Genome centers	• Assembly and mapping in "difficult" regions of the genome • Platform and algorithm artifacts • High-quality benchmark genomes • Performance expectations (sensitivity, specificity thresholds)
Functional variant annotation	• Accuracy of variant annotation, including establishing confidence in genomic landscape of the call	• Documentary standards for critical evaluation of processes, coupled to knowledge of technical platform idiosyncrasies • Data representation standards • Interlaboratory comparisons of annotation • Gold standard annotation of benchmark samples	• Clinical laboratories • Academic laboratories developing methods • Genome centers	• Development of genome-wide "gold standard" annotations
Clinical variant knowledge base (PharmGKB, ClinVar)	• Clinical scope, reliability, relevance, strength, applicability of data in knowledge base	• Documentary standards of evidence for inclusion in knowledge base • Documentary standards for critical evaluation of knowledge base contents, formatting, transaction accuracy • Knowledge base intercomparisons	• Clinicians • Professional societies • Academic laboratories	• Quantitative frameworks to assess knowledge of the strengths of associations of variants and disease • Quantitative framework to assess knowledge base curation/accuracy
Clinical interpretation	• Accurate interpretation of variants, including incidental findings and classification of pathogenicity • Accurate clinical findings	• Documentary standards describing best practices and methods of critical evaluation • Adjudicated benchmark case studies for interlaboratory comparisons of clinical interpretation	• Clinicians • Professional societies • Academic laboratories • Payers	• Quantitative framework to predict performance of clinical interpretation
Reporting	• Accurate and clear reporting of results to clinician in a standard format	• Documentary standards describing reporting guidelines • Interlaboratory comparisons and evaluations of reporting	• Professional societies • Clinicians • Genetic counselors • Clinical laboratories • Payers	• Communicate confidence in findings
EHR archival	• Accurate and interoperable representation of WGS, WES test results	• Data representation standards • Documentary standards describing data representation • Compliance test software to evaluate EHR formatting • Reference implementations	• Payers • Professional societies • HHS • Standards bodies	• No interoperable EHR standards in common practice

to predict the toxicological properties of nanoproducts and nanomaterials. Quantitative structure-activity relationship (QSAR) modeling has been widely used in regulatory decision-making in the risk assessment of drugs and chemicals. QSAR models correlate physicochemical properties of molecules of interest with their undesirable biological activities. Application of a parallel methodology to predict toxicity of products containing nanomaterials has shown promise, with qualitative and quantitative structure-toxicity relationships (QSTRs, or nano-QSARs) derived from the physicochemical properties of nanoparticles (*30*, *31*). These models help prioritize toxicological investigations and might reduce the need for animal testing. A key challenge is the creation of consistent, harmonized, and accessible experimental data standards, as well as the development and validation of physicochemical descriptors of nanomaterials, such as various cellulose-derived polymers.

MODERNIZING THE SCIENCE BEHIND GENERIC DRUG APPROVAL

In 2012, generic drugs accounted for 84% of prescriptions in the United States and less than 30% of total drug spending (*32*). With the dominance of generic drugs in the marketplace, we need a range of methods to support their evaluation. The primary challenge for generic drugs is to be therapeutically equivalent to the branded product. That is, for approval of a generic drug, the FDA Office of Generic Drugs requires that when compared with the branded drug, the generic drug has the same active ingredient, route of administration, dosage form and strength, labeling, and indicated uses for the same patient populations, whereas "inactive" ingredients, manufacturing process, and formulation release mechanisms might differ.

The Office of Generic Drugs has outlined several regulatory science priorities (*33*):

- New standards for bioequivalence. Current approval standards, which tolerate differences in drug exposure of 20% on the same dose, are not sufficient for a drug with a narrow therapeutic index (that is, the therapeutic blood levels are marginally lower than toxic blood levels) (*4*).
- Equivalence of complex products. Many drug products go beyond oral dosage forms to more complex ones, such as drug-device combinations (for example, nasal sprays and insulin pumps) and complex formulations (for example, liposomal drug delivery systems). Simple crossover pharmacokinetic studies in healthy volunteers do not suffice for the approval of complex bioequivalent products. For example, for inhalation or ophthalmic products, which treat a condition locally, it is not appropriate to use pharmacokinetic end points that rely on systemic drug concentrations. Thus, new methods and a set of regulatory guidelines for developing these products would accelerate their evaluation.
- Other unmet needs and challenges. Although generic drugs must contain the same active ingredient, the inactive ingredients may differ. Many of these ingredients have not been tested for biological activity, nor have they been tested for their effects on drug absorption. Bioequivalence measurement standards are needed and represent another potential area of collaboration between NIST and FDA.

ACCELERATING CLINICAL TRIALS

Accelerating the conduct and quality of clinical trials has been a major priority for the drug development industry. Accordingly, new statistical methods and trial designs (for example, designs based on computer simulations and "adaptive" trials that dynamically reassign patients as data are collected) are needed for the rapid conduct and evaluation of clinical trials (*34*). Indeed, recent data suggest that the length of clinical trials has shortened over the past decade, in part because of the use of adaptive clinical trial design; however, these effects on clinical trials may be plateauing (*35*). Beyond trial design and methodologies, there are opportunities for creating an integrated and instrumented electronic infrastructure for storing and accessing patient data that is reliable and easy for clinicians and clinical researchers to use. In particular, clinical trials of new medical products are often conducted across multiple health care systems and involve clinicians and systems that support both patient care and clinical research. Currently, the electronic health record used to support patient care is distinct from the information needed to support clinical investigation, making it burdensome for practicing clinicians to enter data required for the trials. These unwieldy processes pose an enormous barrier for clinical research. Thus, effective standards for complete and high-quality data that can be used for both patient care and clinical research would accelerate clinical trials. FDA recently released a guidance on the use of electronic data in drug development (*36*) and provided funding for eSource, a physician checklist aimed at reducing redundancy when entering clinical research data, improving data quality, and reducing monitoring efforts. When implemented, this checklist will greatly accelerate the conduct of clinical trials across multiple health care systems.

CELL-BASED THERAPY STANDARDS

Standards exist for determining that drug products contain the labeled active ingredients and no contaminants—a basic requirement for small molecules and biologics. In stark contrast, the emerging applications of stem cell–derived products are challenged by uncontrolled product variability and irreproducibility (*37*–*39*). Stem cell–based products often consist of heterogeneous mixtures of cells with complex and diverse properties as well as distinct capacities for differentiation, anatomical distribution, and duration of action. The FDA CBER evaluates submissions for stem cell–based products on a case-by-case basis to determine which tests are appropriate to meet regulatory requirements. However, the increasing pace of submissions has been associated with increasing diversity in product manufacturing, donor and tissue sourcing, cell-surface markers, and other in vitro and in vivo characteristics (*40*). In an effort to facilitate the development of safe and effective cellular therapeutics, the CBER mesenchymal stem cell (MSC) consortium studies human MSC lines derived from bone marrow in order to measure the differences between samples from different donors, as well as the effect of the growth environment on the biological functions of MSCs and their gene expression profiles, differentiation capacities, and epigenetic modifications (*41*–*44*). As a result, MSC consortium members have developed a new immune inhibition assay with which to investigate the immunosuppressive functions of MSCs (*45*), identified cell-surface proteins for cell tracking (*46*), and compiled a database of proteins expressed in MSC lines (*46*, *47*). Future efforts will require methods to assess the complex mechanisms of action of stem cell–based products and to determine critical quality attributes (CQAs) or markers that predict their safety and effectiveness. The use of a core set of standards as well as the same reference materials and databases would facilitate the regulatory evaluation and approval of stem cell–based products (*39*, *48*, *49*).

HIGH-IMPACT SCIENCE

Our summary of unmet needs in regulatory science is not intended to be exhaustive; indeed, it would be impossible to catalog the universe of scientific questions with deep regulatory decision-making implications. Nonetheless, it is apparent that the scientific questions vexing regulators are closely related to the most active research areas for biomedical scientists in both academia and the private sector. Progress in translational research clearly has driven the agenda for research in regulatory sciences, including data science, NGS, new trial design, reproducible cell-based therapies, predictive toxicology, patient-centered decision-making, and long-term device performance. Of course, regulatory science questions ultimately focus on clinical relevance, but on the way to the clinic, there is a compelling need for technologies and methodologies that depend critically on basic biological knowledge.

There has been some reticence among academics to pursue regulatory science, in part from a fear that these questions are only of "niche" interest or would not be sufficiently impactful as compared with basic science discoveries. We find this reticence to be ironic because regulatory science contributions have among the highest potential impacts on human health; they provide knowledge that can directly affect decisions to move molecules, diagnostics, devices, and software into routine clinical practice. Regulatory science is the path through which all impactful technologies of clinical relevance must pass. Training a cohort of scientists who understand how to pose the most important questions for regulatory science and then are equipped to answer them is critical for future progress. Fortunately, the opportunities are compelling, as are the potential contributions to the health of humanity.

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