Advancing nonclinical innovation and safety in pharmaceutical testing

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Nonclinical tests are considered crucial for understanding the safety of investigational medicines. However, the effective translation from nonclinical to human application is limited and must be improved. Drug development stakeholders are working to advance human-based *in vitro* and *in silico* methods that may be more predictive of human efficacy and safety *in vivo* because they enable scientists to model the direct interaction of drugs with human cells, tissues, and biological processes. Here, we recommend test-neutral regulations; increased funding for development and integration of human-based approaches; support for existing initiatives that advance human-based approaches; evaluation of new approaches using human data; establishment of guidelines for procuring human cells and tissues for research; and additional training and educational opportunities in human-based approaches.

Introduction

Before an investigational drug can be evaluated in a clinical trial, the US Food and Drug Administration (FDA) requires that drug sponsors provide toxicological, pharmacological, and pharmacokinetic nonclinical data [1]. This information is considered crucial to understanding potential human outcomes before testing in humans (www.fda.gov/ForPatients/Approvals/Drugs/ucm405658.htm). However, ~96% of potential new medications that successfully complete nonclinical tests fail in human studies for reasons that include safety [2]. These failures place patients at

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risk and contribute to the rising cost of drug development through late-stage attrition, leaving ample opportunity for improvement. Consequently, there is a large unmet need for nonclinical approaches that can predict human outcomes more effectively than those test methods currently being used.

Towards more predictive nonclinical tools

Over the past few years, the FDA has initiated several efforts in the USA to improve the tools and approaches used for nonclinical safety assessment, recognizing that the development of new methods is core to the regulatory mission of the agency. In 2011, the FDA released a strategic plan, *Advancing Regulatory Science at FDA*, which included 'modernizing toxicology to enhance product safety' among its eight priorities. As part of that plan, the FDA participated in collaborative research efforts with the Defense Advanced Research Projects Agency (DARPA), the National Center for Advancing Translational Sciences (NCATS), other centers and institutes of the National Institutes of Health (NIH), academic institutions, nonprofits, and the regulated industry to advance predictive toxicology. Most recently, in December 2017, the FDA unveiled a Predictive Toxicology Roadmap as a high priority [3].

In Europe, the focus has been on integrating the '3Rs' of replacement, reduction, and refinement of animal tests used for regulatory consideration in accordance with Directive 2010/63/EU. In 2010, the European Medicines Agency (EMA) formed an expert group to provide input on animal testing for human drugs to the Committee for Medicinal Products for Human Use (CHMP) [4]. In 2016, a smaller working group followed and adopted a guideline on the regulatory acceptance of '3Rs' testing approaches that highlights replacement as the ultimate goal and describes the process for regulatory acceptance of new technologies [4].

International efforts to improve pharmaceutical test methods include organizations dedicated to the 'validation of alternative methods', such as the United States Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), the European Union Reference Laboratory for Alternatives to Animal Testing (EURL ECVAM), the Japanese Center for the Validation of Alternative Methods (JaCVAM), and the Canadian Centre for the Validation of Alternative Methods (CaCVAM). Although each of these validation centers has a unique mission, efforts at each center include evaluating new methods to be integrated into pharmaceutical testing that are equal to, or better than, current methods. Scientific societies, such as the European Society for Alternatives to Animal Testing (EUSAAT) and the American Society for Cellular and Computational Toxicology (ASCCT), provide a platform for sharing expertise, networking, and learning about new methods. '3Rs' centers that all include efforts to replace the use of animals with more predictive tests continue to emerge around the globe and are currently located in the UK, Switzerland, The Netherlands, Italy, Slovenia, Germany, and Sri Lanka.

In addition to these efforts, the NIH, pharmaceutical industry, science and technology companies, and academic researchers are all working to develop methods suitable for adoption in the regulatory context. Additional work focusing on law, regulation, policy, science, training, and education is needed to ensure that these methods are appropriately evaluated and implemented, because use of improved nonclinical methods should increase the efficacy and efficiency of drug development. As a result, quicker approval of beneficial new drugs and better safeguarding of clinical trial participants and the patient populations should be accomplishable.

The tools used in the ongoing quest for the discovery, development, and delivery of new treatments for human diseases have begun expanding to include human-based *in vitro* and *in silico* nonclinical approaches that simulate biological and physiological interactions that occur in humans *in vivo*. The Predictive Toxicology Roadmap of the FDA, which aims to integrate new approaches while reducing animal tests, lists the following human-based methods as especially promising new technologies for use in predictive toxicology: microphysiological systems; alternative test methods for reproductive toxicity testing; computational toxicology; *in vitro* alternatives; and read-across methodologies [3]. Although evaluation of these methods is crucial to understanding their value in predicting human *in vivo* outcomes, human-based approaches can be expected to provide data that are more relevant than animal-based methods because they enable scientists to investigate how drugs interact with human cells, tissues, and biological processes directly, removing the need for cross-species extrapolation.

Considering the individual patient

Parallels could be drawn between the recent recognition that greater human relevance is needed in the nonclinical space and the new emphasis on real-world data (RWD) and patient-focused drug development that is emerging in the clinical development and postmarket settings. The idea that assessment of safety and efficacy should be informed by data that are as relevant to and representative of, diverse patient populations in 'real-world' settings represents a fundamental shift in the approach to drug development and approval. Studies in precision medicine have revealed the heterogeneity of individual patients based on personal genomics and individual differences in lifestyle and environmental exposures that create diversity in patient characteristics not present in current nonclinical models. Additionally, there is increasing recognition that most patients take more than one drug (*i.e.*, polypharmacy) and have more than one disease (*i.e.*, comorbidities), which will need to be considered to improve the transferability of nonclinical testing to real-world patients [5]. This shift away from relying on what is easier and 'clean' to measure, or what has been measured historically, has been enabled by significant advancements in science and technology as well as a growing social awareness that we can do a better job for patients.

Here, we describe a collaborative initiative formed to advance the field of nonclinical testing by recommending actions that support the development and use of human-based nonclinical approaches. The initiative has expanded from its initial USA focus, recognizing that international collaboration will be key to integrating new tests. Although developed before the release of the Predictive Toxicology Roadmap of the FDA, these recommendations are highly complementary.

Nonclinical innovation and patient safety initiative

On January 11, 2017, the Physicians Committee for Responsible Medicine (Physicians Committee) hosted a roundtable with a

group of expert stakeholders from federal agencies, the pharmaceutical industry, technology companies, academia, and patient, research, and health organizations to discuss challenges and opportunities to improve the human-relevance of nonclinical testing. On March 15, 2017, DiscoverX (now Eurofins DiscoverX) and the Physicians Committee hosted an ancillary meeting at the Society of Toxicology Annual Meeting that provided a forum for additional scientists to join the conversation. On March 13, 2018, in-person discussions continued as InSphero AG and the Physicians Committee hosted another ancillary meeting at the Society of Toxicology Annual Meeting. These discussions focused on law, regulation, policy, science, training, and educational opportunities, and were guided by the questions listed in Box 1.

Recommendations for improving the human relevance of nonclinical testing

The following recommendations arose from participant discussions at the roundtable, ancillary meetings, and follow-up conversations.

Change policy requirements for 'animal' data to 'nonclinical'

Law, regulation, and policy must support innovative science. Those that do not maintain pace should be updated. Current FDA regulations mandate animal data in many instances, despite the commitment of the FDA to transforming toxicology, as described in the Predictive Toxicology Roadmap [3]. Federal agencies around the globe, including the FDA, EMA, and the Pharmaceuticals and Medical Devices Agency (PMDA) of Japan, should review and update any regulations that do not reflect discretion to accept information provided by human-relevant nonclinical methods. Changing any requirements for 'animal' data to 'nonclinical' would offer flexibility that accommodates evolving science, signal to the pharmaceutical industry that human-based methods are accepted, and will help ensure the longevity of the regulations in the face of rapidly advancing human-based nonclinical approaches. Efforts focused on the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) may be warranted, because the ICH seeks to harmonize the way in which medicines are developed worldwide; the USA, Europe, Japan, Brazil, Republic of Korea, Singapore, China, and Taiwan are all members that commit to implementing recommendations of the ICH. However, original, regional regulations must also be updated.

BOX 1

Discussion Questions on Legal, Regulatory, Scientific, Training, and Educational Opportunities

What are the barriers to acceptance of new approaches to assessing toxicity? How can we overcome them? What role can the Federal Government take in leading or promoting the exploration of new approaches for evaluating the safety of medical products? How can the pharmaceutical sector draw from success in the chemical sector? What law and policy concerns must be addressed to support innovative nonclinical testing? What scientific opportunities exist to improve nonclinical testing? What training and educational programs exist? What other types of program should be developed? How can stakeholders collaborate to advance the field?

In the USA, recent FDA actions indicate that the agency may be amenable to making these regulatory updates. In September 2017, the FDA announced that a Regulatory Reform Task Force would review existing regulations, and sought input to identify outdated regulations that should be updated or deleted. In December 2017, an FDA Voice blog addressing 2018 policy goals highlighted efforts to modernize regulatory standards and ensure the use of the latest science. However, a multifaceted approach of working with the FDA and Congress, and/or the ICH directly should be embarked upon to ensure a timelier policy change. International collaborations will help accelerate new technologies faster, because industry may be resistant to integrating a new technology that is accepted in some jurisdictions but not others, when the traditional animal tests are accepted across jurisdictions.

Increase funding for development of human-based approaches

During a congressional hearing in 2016, the Director of the NIH, Francis Collins, stated that animal safety testing for drugs would largely be replaced by new technologies, such as induced pluripotent stem cells and microphysiological systems, within 10 years (www.appropriations.senate.gov/hearings/hearing-on-fy2017-national-institutes-of-health-budget-request. The quote is in the video on the page at minute 33:45–34:25, but not the written transcription). To move quickly and responsibly toward this goal, funding agencies should prioritize funding and support for the development and evaluation of human-based approaches. Grant reviewers around the world may need training and education in the value and opportunity provided by such human-based approaches to help increase grant funding for their development and evaluation. In the USA, reviewer training could be established by the NIH or provided by external stakeholders. New study sections could be formed with experts in the field of human-based methods.

Support existing initiatives that aim to improve nonclinical approaches

Multiple current initiatives aim to improve the nonclinical methods that are available for the evaluation of new medicines. The broader drug development stakeholder community should support these initiatives because improved methods help all stakeholders meet their goals.

In December 2017, the FDA unveiled its Predictive Toxicology Roadmap, which aims to transform the development, evaluation, and integration of new toxicology methods across FDA centers [3]. The Roadmap acknowledges the scientific advances made since the 2007 National Research Council of the US National Academy of Sciences report, *Toxicity Testing in the 21 st Century, A Vision and a Strategy,* which recommended moving from animal-based tests toward more predictive and human-relevant approaches, and establishes a plan for support and implementation. The six-part framework includes an organizing committee, training, communication, collaboration, research, and oversight. In September 2018, the FDA held a public hearing to receive input on how to better work with stakeholders as it begins roadmap implementation. At the hearing, the Physicians Committee offered to sponsor regulator training on human-based approaches as a start to roadmap implementation as well as coordinate stakeholders or other

experts who can communicate industry perspectives, identify gaps in research, and recommend approaches for acceptance.

Additionally, the FDA initiated a collaborative public–private partnership, called PredicTox, to improve patient safety by exploring a systems pharmacology approach that goes beyond traditional nonclinical testing to mechanistically understand drug-induced adverse events from the cellular level to the clinical phenotype. If successful, this approach will lead to better prediction of drug-induced serious adverse events, better nonclinical screens to identify problems early during drug development, better clinical risk diagnostics (safety biomarkers), and gain biological and/or mechanistic insights to help validate safety signals from marketed products.

In 2011, the NIH increased its focus on more predictive approaches with the establishment of NCATS [6]. Through the Tissue Chips for Drug Testing program, NCATS and its partners have developed and linked a ten-organ microphysiological system to be explored for use in drug testing. Stakeholders should continue supporting this project by contributing compounds, human data, and resources for evaluation of the tissue chips.

ICCVAM is working to improve the validation of human-based methods as part of its strategic roadmap for evaluating the safety of chemicals and medical products (including pharmaceuticals) in the USA. The ICCVAM roadmap and corresponding efforts are being developed in conjunction with federal research and regulatory agencies along with broad stakeholder input (https://ntp.niehs.nih.gov/pubhealth/evalatm/natl-strategy/index.html). Stakeholders should take advantage of opportunities for written and oral public comment, and offer to support ICCVAM validation activities in ways that coincide with the goals of the organization. The types of support needed will cover a variety of stakeholders and include public–private partnerships, precompetitive collaborations to develop shareable data, models and protocols, fit-for-purpose method development, validation practices that engage end-users, coordination with personalized medicine initiatives and associated expert guidance, and obtaining compounds with human data to be used in reference sets.

The Innovative Medicines Initiative (IMI) in Europe is a public–private partnership that works to speed development and access to innovative medicines, in part by improving the current drug development process by supporting development of new tools to assess safety and efficacy. The eTox project of the IMI resulted in eTOXsys, a novel computational method for predicting safety profiles by integrating existing public and private toxicological data. After the successful completion of this project, IMI initiated a follow-up project in 2017 called eTRANSAFE, which will integrate nonclinical and clinical data to analyze the predictive robustness of animal studies (*i.e.*, translational safety; http://etransafe.eu/). Stakeholders should monitor other ongoing projects that seek to improve *in vitro* and computational methods [7].

Support assessment activities that incorporate human data

Generally, product-specific evaluation of the applicability, limitations, relevance, reliability, reproducibility, and sensitivity of a new approach must be shown before that method will be accepted for regulatory purposes [3]. Such an evaluation process can also help industry and regulators gain confidence, yet can also act as a barrier to progress because the onus is on the company to prove a method is valid, despite a lack of clear and publicly available evaluation standards in many cases. This is of particular concern because current nonclinical animal-based methods are poorly validated for human predictivity and relevance, and there is substantial evidence of a lack of good concordance [8–11].

Historically and ironically, human-based approaches have been evaluated for their ability to predict animal toxicity, rather than human toxicity [12]. This is a major ongoing obstacle that must be addressed, because new, human-based methods may be rejected for failing to predict the result of an animal test that might itself be incorrect. One possible approach is through use of real-world evidence (RWE). RWE is defined as clinical evidence regarding the use and potential benefits or risks of a drug derived from analysis of RWD. RWD is defined as data related to patient health status and/or the delivery of healthcare routinely collected from a variety of sources [13]. The 21 st Century Cures Act and Prescription Drug User Fee Act VI require the FDA to explore the expansion of uses of RWE. Efforts should be made to expand that focus from postapproval to include availability of clinical data and RWE and/or RWD to method developers for design and evaluation purposes. Drawbacks to RWD, such as the quality and standardization of data, should be considered in study design.

Establish tissue-recovery guidelines to increase access to high-quality human cells and tissues for research

The use of human-based approaches requires that researchers have access to human cells and tissues. The supply of high-quality human cells and tissues that are available for research purposes will need to increase to meet demand. Currently, there are no guidelines for the collection and care of human cells and tissues that will be used for research, and we are unaware of efforts to establish them. Private stakeholders should work together with federal partners to address this issue immediately so that clear and comprehensive guidelines are established. The Physicians Committee held a roundtable to begin stakeholder discussions on this and other relevant human tissue considerations in October 2018.

Create a central hub to communicate existing training, funding, and educational opportunities in human-based regulatory science and/or new approaches

A comprehensive, centralized source for communicating public-facing efforts would create efficiencies to optimize limited resources and encourage interest and engagement. This hub could take the form of a web portal that communicates upcoming opportunities, archives recorded trainings, lists grant awards, provides consensus white papers, and lists graduate programs, certificates, and fellowships in regulatory science, which the FDA defines as 'the science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of all FDA-regulated products' [14]. Stakeholders should explore whether the National Library of Medicine or a different organization would be the ideal candidate for hosting the hub.

Develop additional training and educational opportunities in human-based nonclinical approaches

In addition to the regulator training highlighted in the Predictive Toxicology Roadmap of the FDA, the new generation of

scientists must be supported as they seek careers in human-based regulatory science. The field of regulatory science is growing, and limited opportunities already exist in the form of certificates, degrees, coursework, and fellowships [15]. To prioritize and facilitate development of new tools to answer regulatory questions, regulatory science should be treated as a discipline within graduate schools. This will create an avenue for more scientists to enter the field. In 2011, the FDA released a strategic plan for advancing regulatory science that included developing better nonclinical models of human adverse responses, partially by evaluating and promoting the use of cell- and tissue-based assays that might more accurately predict human adverse reactions [8]. Accordingly, human-based nonclinical approaches should be adequately represented in efforts to develop the educational discipline.

The Regulatory Science Workgroup, a broad group that originally initiated as part of the NIH Clinical and Translational Science Award (CTSA) Network, has already begun working to develop regulatory science as a discipline by identifying and developing core competencies (including nonclinical), as well as curriculum guidelines [16]. Stakeholders should work to ensure that the nonclinical competency prioritizes human-based approaches.

The Centers for Excellence in Regulatory Science and Innovation (CERSI) of the FDA provide additional opportunities to expand and further develop efforts in human-based nonclinical methods. The FDA has established five CERSIs to advance regulatory science that foster collaborations between the FDA and academia in research, education, and professional development [9]. CERSIs could provide an avenue to help the FDA implement its goal of transforming toxicology and, therefore, should expand to include the human-based nonclinical aspect of regulatory science and a network for data sharing. Stakeholders should work with existing CERSIs to determine whether there is interest in establishing research projects and/or fellowships to evaluate or implement human-based nonclinical approaches before working to establish a CERSI.

Concluding remarks

Although traditional animal-based tests are the current norm for assessing nonclinical drug safety and efficacy, modern human-based approaches are becoming more prevalent and should be prioritized. As more predictive tests are used earlier in the testing process, unsafe or ineffective treatments will fail faster and potentially useful drugs will not be discarded because of false toxicity determinations, resulting in reduced waste, cost, and animal use. The Nonclinical Innovation and Patient Safety Initiative complements the Predictive Toxicology Roadmap of the FDA and aims to ensure that scientists have the best possible tools to evaluate potential medicines, thus contributing to the timely delivery of safe and effective treatments. International collaboration among federal governments and drug development stakeholders on legal, regulatory, policy, scientific, training, and educational opportunities is essential to ensure that the field advances as quickly and as responsibly as possible, while maintaining a regulatory environment in support of safe and effective drug development.

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