Testimony of

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The Center for a Humane Economy, Animal Wellness Action, and Animal Wellness Foundation,

Before the Subcommittee on House Committee on Energy and Commerce

Thursday, February 29, 2024

"Legislative Proposals to Support Patients with Rare Diseases"

This testimony highlights key facts related to the FDA Modernization Act 3.0 (H.R. 7248) and expresses our enthusiastic support for this bill. We describe the benefits conferred by the proposed legislation and the urgent need for it at this time, especially in the context of the FDA Modernization Act 2.0 (FDAMA 2.0) becoming U.S. law in late 2022. As the honorable committee members explore legislative proposals to support patients with Rare Diseases, we hope that this information provides additional clarity and aid deliberation.

Summary of Features and Benefits of the FDA Modernization Act 3.0 (H.R. 7248)

The enactment of H.R. 7248 directly benefits patients with rare, serious, and life-threating diseases. At its core, the bill delineates a path to improve the crushing failure rate in drug development (95%) by leveraging innovative and reliable technologies. It reduces fiscal waste caused by the indefensible spending on poor-predictive-value models (like animal models) in favor of better New Approach Methodologies (NAMs). Finally, the bill facilitates the consolidation of disparate, fragmented resources at the FDA towards improving transparency and bolstering regulatory approvals, including time, efficiency, and output.

A hallmark of H.R. 7248 is its feasibility as a budget-neutral investment, requiring no new funds. Instead, the enactment of the bill will allow more efficient use of existing resources at the FDA, given the relief it creates to existing programs such as the oversized and demanding 'Animal model qualification program.' According to the FDA, "…significant delay in our DDT [Drug Development Tool] qualification reviews at CDER [is] due to an overall increase in the DDT Qualification Program workload (…)" The agency has been forthcoming about inefficiencies in regulatory review, as described. Briefly, when qualified NAMs exist to guide the drug development process, the need by drug developers to seek qualifications for animal models shrinks. Qualifying NAMs can radically reduce the backlog of the Animal model qualification program over time and as such add value to the FDA and sponsors alike.

Currently, over 7,000 rare diseases affect between 25-35 million Americans—and 95% of those diseases have FDA-approved drugs. The poor reliability of animal models compounds sky-high R&D costs to disincentivize investment in this area. In addition, most new-generation therapies (e.g., cell therapy, immunotherapy) are very human specific by design, hence their promise. They cannot and should not be recapitulated in other species. For Rare Diseases in particular, the innovative 21st-century methods stipulated in the FDAMA 3.0 (and FDAMA 2.0) are among the most promising frontiers. Examples include the use of organ chips to understand Barth Syndrome, 3D models (organoids) of the midbrain for characterizing NGLY1 deficiency (a rare neurological disease), and artificial intelligence (AI) tools in developing treatments for Fragile-X syndrome.

An Urgent Need for FDAMA 3.0 (H.R. 7248) in the Aftermath of FDAMA 2.0

On Dec. 29, 2022, the FDA Modernization Act 2.0 (FDAMA 2.0) became law as Sec. 3209 of the Consolidated Appropriations Act, 2023. FDAMA 2.0 made animal testing of investigational new drugs (INDs) optional by expanding the definition of "nonclinical test" to include modern 21st century methods or NAMs like cell-based assays, organ chips, organoids, computer modeling, and bioprinting. The goal was both to make drug testing more humane and to speed drug development. According to the National Center for Advancing Translational Sciences (NCATS), one of the centers within the NIH, the animals-only regime has led to a 95% failure rate for new drugs,[1] which wastes precious time for patients.

Regrettably, more than a year after FDAMA 2.0 was signed into law, little to no change has been created by the agency to practically translate such major development into meaningful practice. For instance, FDA has yet to demonstrate a sincere rulemaking effort to conform policy to the statute. This is causing marked regulatory confusion. In addition, the agency has ignored inquiries from nine lawmakers in the Senate who raised serious concerns and demanded explanations for such inaction through a letter addressed to FDA commissioner. Rulemaking is a critical step in implementing enacted U.S. laws, especially in complex health related matters. In turn, compliance with the law by federal agencies is not optional or discretionary.

The refractoriness by the Agency stands in stark contrast to the expectations, let alone excitement, that ensued following the signing of the new law in late December 2022. Since then, more than 460 worldwide publications, including news articles, commentaries, scientific reviews, and primary papers have been published, underscoring the transformative nature of the FDAMA 2.0 and its mighty importance. Naturally, many stakeholders assumed that the FDA would rush to embrace the new reforms which are aiming, first and foremost, at improving the safety and efficacy of the drug development process, a core responsibility of the agency.

[1] National Institutes of Health, National Center for Advancing Translational Sciences (NCATS), "New Therapeutic Uses": https://ncats.nih.gov/research/research-activities/ntu. Accessed 28 Jan. 2024. Additionally, federal regulations already recognize that "animal reproduction studies are not always predictive of human response." *See* 21 C.F.R. §201.80(f)(6)(i)(b).

The current paradigm of drug development yields a crushing 90-95% failure in clinical trials of the very experimental drugs that advanced based on animal testing. Such failure to act not only causes precious delays in critical drugs reaching the market but also squanders money, efforts, talent and hopes for effective treatments and life-saving cures for millions. Continuing down the path of the existing drug discovery paradigm is nothing short of perpetuating a futile cycle and is highly irresponsible.

A Clear Path for Qualification of NAMs as Proposed is Vital for Progress

A critical aspect in the regulatory review of experimental drugs is the qualification program of methods, measures, and materials, collectively termed Drug Development Tools (DTTs). According to the FDA "Having qualified DDTs that can be used by many sponsors helps optimize drug development and evaluation." On qualification, the FDA provides the following definition: "Qualification is a conclusion that within the stated context of use, the DDT can be relied upon to have a specific interpretation and application in drug development and regulatory review. Once qualified, DDTs will be publicly available to be used in any drug development program for the qualified context of use. Additionally, the qualified DDT generally can be included in IND, NDA, or BLA submissions without needing FDA to reconsider and reconfirm its suitability."

As such, a qualification program for NAMs is vital to incorporate the use of such tools in the current paradigm of drug development. Currently, the FDA has three established qualification programs. In addition to the above-mentioned 'animal model qualification program', the biomarkers program and the clinical outcome assessments program constitute the other two. Unfortunately, FDA programs that qualify NAMs are cursory, ineffective, and lack transparency.

The FDAMA 3.0 urges the FDA to leverage and consolidate disparate resources to establish a qualification process for NAMs. Indeed, the agency has a unique opportunity to capitalize on the resources, lessons learned, and interagency efforts, including existing networks focused on NAMs (e.g., ICCVAM) as well as resources appropriated through pilot programs.

For instance, the Innovative Science and Technology Approaches for New Drugs (ISTAND) Pilot Program has been in existence now for several years. It was established as a result of a congressional inquiry by the Office of Government Accountability (GAO, report date 2019) with the intent to improve interagency cooperation in this emerging domain. A pilot program, as the name implies, is exploratory. It is neither intended nor expected to be open-ended.

It is also safe to assume that what the FDA stipulated in the pilot phase of ISTAND anticipating accepting "2-4 submissions in the ISTAND pilot program each year with a triage and selection process that focuses on public health impact and feasibility of implementation" is incompatible with the spirit of innovation in a competitive capital market. The applications solicited and processed by the FDA on NAMs must count in the hundreds, not "2-4 submissions."

The NAMs qualification effort stipulated in FDAMA 3.0 is a logical next step to consolidate resources, eliminate redundancy, and reduce fiscal waste among well-intended but scattered

pilots aiming at advancing innovative Science and Technology approaches. Its realization will establish a tractable effort, akin to the other three FDA qualification programs, with the full transparency, accountability, and oversights that such federally established programs entail.

Executing Public Policy is not Optional and Requires Modest Efforts from the FDA

Amending regulations to conform to a statute passed by Congress is a routine task for any agency, regardless of whether a statutory deadline is imposed. The FDA has had a longstanding public commitment to the "3 Rs": 1) reducing the number of animals used in research, 2) replacing animal methods where superior ones are available, and 3) refining techniques to minimize animals' pain and distress. This is why FDAMA 2.0 did not mandate a preference for nonanimal testing methods; that preference already exists in agency policy. This is also why Congress did not consider it necessary to impose a deadline for rulemaking.

Changing the regulations, as a legal and technical drafting exercise, will require limited investments of time and resources. It has now been 14 months and FDA hasn't commenced that effort. When it comes to an agency rewriting regulations, this is as simple as it gets, and the work product was handed off to the key agency personnel months ago.

Dozens of regulations continue to call for animal tests without offering drug sponsors any other option. The plain language of FDAMA 2.0 was straightforward and not complex, opening the drug approval process to 21st-century human-biology-based screening methods. In this case, the revisions that FDA must make to its regulations for drug sponsors are also very straightforward. We itemized the conflicting regulations in Exhibit A.

The FDAMA 3.0 (H.R. 7248) is Feasible with No Burden to the Agency or Appropriations

- *No new infrastructure is needed at the Agency beyond existing resources*. In fact, no capital investments or infrastructure development are required given the largely review and assessment nature of this qualification effort - a scholarly exercise, first and foremost. Assessment and evaluation of standards is the core expertise of the agency and its qualified staff. In-house talent at the FDA (e.g., toxicology experts) or trusted outside reviewers are routinely solicited to review applications and serve on special emphasis panels at the FDA as needed. Experts evaluate applications based on FDA-qualified models and applicable standards. Such intellectual and largely academic activities represent the bulk of what is needed for the implementation of non-animal testing qualification efforts. Expertise and talent at the agency and its ecosystem are already existent, if not abundant.

The FDA Modernization Act 3.0 (H.R. 7248) will create value by requiring:

  - FDA to publish a final rule to implement FDAMA 2.0.
  - HHS to establish a process to qualify nonanimal methods that either improve predictivity for safety and effectiveness or reduce development time.

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- a public meeting and comment period, followed by guidance on the non-animal qualification process.
- FDA to submit an annual report analyzing the success of the qualification process with an estimate of how many animals it saves.

- *No new functions or responsibilities expected from the Agency beyond its current mandate.* The onus is on applicants seeking regulatory approvals to make convincing arguments and present in their applications the sufficient data gathered from relevant testing models. It is the sponsor's responsibility, not that of the FDA, to support the safety and efficacy of an experimental drug proposed. The role of the FDA is to qualify methods rendered permissible by law that are innovative and might offer equal or better value to existing schemes. In this context, the FDA acts as an objective judge of the work of others. The FDA's role and function in the case of non-animal testing qualification effort stipulated in FDAMA 3.0 is - not unlike - its routine and daily activities within the other FDA-established qualification programs (namely, the Animal model qualification program, the Biomarker Qualification program, and the Clinical Outcome Assessment Qualification program).

To Improve Drug Development, Congress Must Take Action to Implement FDA Modernization

H.R. 7248 is a public health bill, focusing on the implementation of the FDA Modernization Act 2.0 to address the problems with the current drug development model.

- Animal tests, in large part, are not predictive of the human response to drugs, with 90 to 95 percent of drugs and vaccines found safe in animal tests failing during human clinical trials.
- Most diseases have no treatment available. Adverse drug reactions are the fourth highest cause of death in the U.S. Use of human biology-based test methods would better predict how humans will respond to drugs in clinical trials.
- In addition to falsely identifying a toxic drug as "safe," animal tests can falsely label a potentially useful therapeutic agent as toxic. Thus, of the many thousands of drugs that have failed in animal tests, some might have worked in humans.
- The reduction in the number of false negatives (FN-drugs that are toxic but predicted by animal tests to be safe) directly increases consumer safety. Decreasing the rate of false positives (FP-drugs that are safe but predicted to be toxic) has a direct effect on productivity and allows the marketing of products that would otherwise have been filtered out. The effect of allowing for safer products (low FN rate) and more marketable products from the discovery process (low FP rate) means increased business profit.
- A recent Phase 2b human clinical trial of Johnson & Johnson's HIV/AIDS vaccine failed because of lack of efficacy. Animal data had shown 90% efficacy.[2] This is consistent with the 30+ year effort to develop a HIV/AIDS vaccine. The animal data show promise, but the vaccines do not work in humans.

[2] J &J's HIV vaccine fails phase 2b, extending long wait for an effective jab, Fierce Biotech, August 31, 2021 https://www.fiercebiotech.com/biotech/j-j-s-hiv-vaccine-fails-phase-2b-extending-long-wait-for-effective-jab and https://www.statnews.com/2021/08/31/first-efficacy-trial-of-johnson-johnsons-hiv-vaccine-fails

- On September 2, 2021, FDA's Cellular, Tissue, and Gene Therapies Advisory Committee said animal models are "problematic" in assessing the safety risks of gene therapies derived from adeno-associated virus (AAV) vectors. There have been "severe" adverse events in AAV vector clinical trials, including instances of acute liver and kidney failure in children. One third of the 500 children under the age of 2 treated with Zolgensma had at least once adverse event of hepatoxicity.[3]
- Studies show that while toxicity in animals may also be present in humans these tests are not consistent or reliable and provide nearly no insight into the possibility or likelihood of toxicity or the absence of toxicity in humans.[4]
- In one protocol, researchers studied six drugs to determine which of the 78 adverse effects that occurred in humans would occur in dogs or rats. Effects that are undetectable in animals (e.g., headaches) were not considered. Less than half (46%) of the remaining side effects were.
- detected in the animals - slightly less than the expected results from flipping a coin. In other words, animal tests were wrong 54% of the time.[5]
- Another study of drug registration files was conducted to determine whether post-marketing serious adverse reactions to small molecule drugs could have been detected based on animal data. Of 93 serious adverse reactions related to 43 small molecule drugs, only 19% were identified in animal studies as a true positive outcome.[6]

Aside from the little relevance to humans, animal data is very costly to generate:

- The cost for developing a single new drug may be from $1 - $6 billion, and the average timeline of development of a potential drug and vaccine from the lab to market is 10—15 years.
- Estimates suggest that, relative to *in vitro* models, animal testing is 1.5 to 30 times more expensive.[7]

[3] Animal models have limitations for safety assessment of gene therapies: FDA adcomm, Regulatory Focus, September 2, 2021. https://www.raps.org/news-and-articles/news-articles/2021/9/fda-adcomm-points-to-limitations-of-animal-studies?utm_source=MagnetMail&utm_medium=Email%20&utm_campaign=RF%20Today%20%7C%202%20September%202021

[4] Bailey, J., Thew, M., Balls, M., An Analysis of the Use of Dogs in Predicting Human Toxicology and Drug Safety, *Alternatives to Laboratory Animals,* 2013, 41(5), pp. 335-350., Bailey J, Thew M, Balls M., An analysis of the use of animal models in predicting human toxicology and drug safety. *Alternatives to Laboratory Animals*, 2014;42:189–99., Bailey, J., Thew, M., Balls, M., Predicting Human Drug Toxicity and Safety Via Animal Tests: Can Any One Species Predict Drug Toxicity in Any Other, and Do Monkeys Help? Alternatives to Laboratory Animals, 2015, 43 (6), pp,393-403.

[5] Clin Pharmacol Ther 1962; pp665-672 https://doi.org/10.1002/cpt196235665

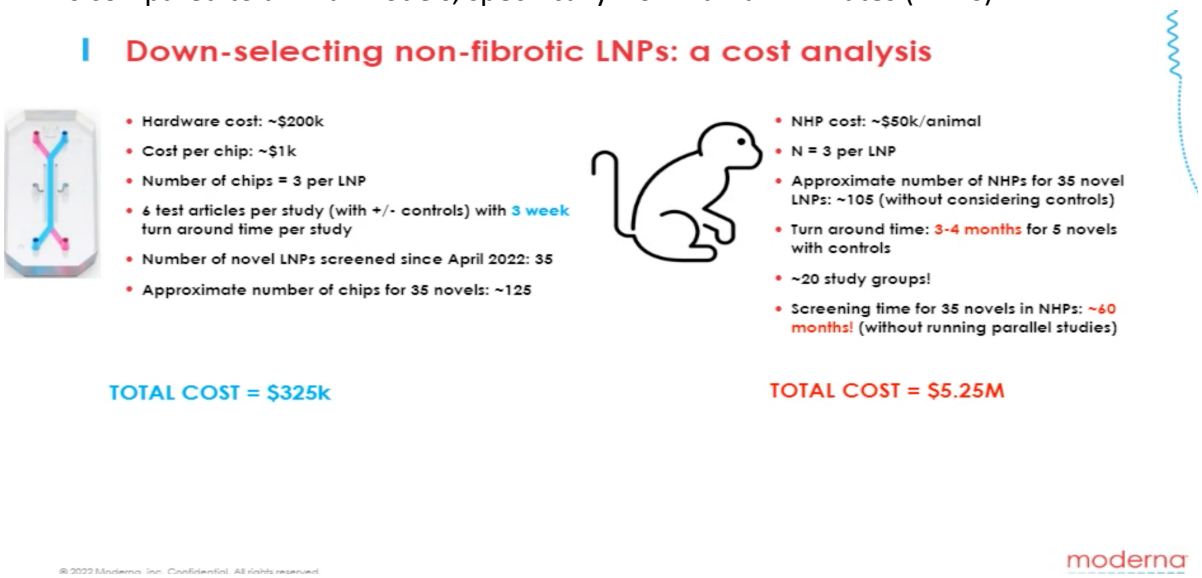
[6] Van Meer, P,J., Kooijiman, M., Gispen-de Wied, CC., Moors, E.H., Schellekens, H. The Ability of Animal Studies to Detect Serious Post Marketing Adverse Events Is Limited, *Regulatory Toxicology and Pharmacology*, 2012, 64 (3), pp. 345-349

[7] Rodent testing in cancer therapeutics adds an estimated 4 to 5 years to drug development and costs $2 to $4 million. Compared with the costs of in vitro testing, **animal tests range from 1.5× to >30× as expensive.** Limitations of Animal Studies for Predicting Toxicity in Clinical Trials: Is it Time to Rethink Our Current Approach? https://www.sciencedirect.com/science/article/pii/S2452302X1930316X

- The Emulate study (see next section), included an economic evaluation indicating routine use of the Emulate Liver-Chip to identify liver toxicity risk in small-molecule drug development could generate approximately $3 billion per year by driving an increase in research and development productivity. Regulatory acceptance of NAMs would provide drug sponsors more options for testing the safety and efficacy of drugs to improve clinical trial attrition rates, cut time to market in half, and substantially reduce R & D costs which could cut drug prices fivefold.[8]

<u>Human Relevant Models are Key to Improving the Drug Development Process</u>

- Analysis from the company Moderna in 2023 shows a significant economic benefit for using NAMs compared to animal models, specifically Non-Human Primates (NHPs). [9]



- In a recent study,[10] researchers assessed the performance of 780 human Liver-Chips across a blinded set of 27 known hepatotoxic and non-toxic drugs. In line with the IQ MPS guidelines, the tested drugs included seven matched pairs that demonstrate the chip's ability to distinguish toxic drugs from their less-toxic structural analogs. **Furthermore, the study demonstrated that the Emulate Liver-Chip was able to correctly identify 87% of the tested drugs that caused drug-induced liver injury in patients despite passing through animal testing**. At the same time, the Liver-Chip did not falsely flag any drugs as toxic, supporting its

[8] Marx, U., Andersson, T. B., Bahinski, A. et al. (2016). Biology-inspired microphysiological system approach to solve the prediction dilemma and substance testing. *ALTEX* 33, 272- 321. doi:10.14573/altex.1603161

[9] https://emulatebio-1.wistia.com/medias/fqblwxqfdq?hstc=68085326.27f8e5da2651d3dbeaf1e049d64894c3.1700521025313.1700521025313.1700521025313.1&hssc=68085326.1.1700521025313&hsfp=1723886671&submissionGuid=a73526a2-7ad0-468c-ad1e-187f664f887f at 12:32. "Down-selecting non-fibrotic LNPs: a cost analysis OOC (organ on chip) Liver chip" Moderna

[10] Ewart, L., Apostolou, A., Briggs, S.A. *et al.* Performance assessment and economic analysis of a human Liver-Chip for predictive toxicology. *Commun Med* **2**, 154 (2022). https://doi.org/10.1038/s43856-022-00209-1, https://www.nature.com/articles/s43856-022-00209-1

use in toxicology screening workflows. In comparison, published data for 3D hepatic spheroids shows a sensitivity rate of 42% and a specificity rate of 67% for the same drug set.

Additional Background on Prior Petitions and Earlier Responses From the FDA

- *For Nealy a Decade, FDA Has Stonewalled Legal Petitions Seeking Agency Support for Regulatory Updates to Clarify that Nonanimal Tests Are Permitted in Nonclinical Trials:*

Fifteen years ago, FDA received a thoroughly presented citizen petition specifically requesting a regulatory change to allow the use of data from non-animal methods. Three years later in response, FDA said it would issue draft guidance, but later moved decided not to do so. Nine years ago, another citizen petition seeking discretion to use such data was filed in 2015. While FDA provided two "interim responses," FDA has not yet provided a substantive response as required by 21 CFR 10.20(f).

- *Modification of Regulations Petition Related to Animal Testing – FDA-2015-P-2820- July 2015:*

In July 2015, the Center for Responsible Science, with a series of other co-petitioners[11] requested that FDA modify existing regulations in Title 21 of the Code of Federal Regulations (CFR) that govern requirements for investigational new drug (IND) applications, investigational device exemptions (IDE), and new drug applications (NDAs).

Specifically, petitioners requested that Commissioner of the FDA amend certain regulations to establish and clarify that FDA will accept data from scientifically recognized modern and emerging test methods to support a drug or device investigational application. The requested amendments would broaden options in nonclinical testing and will not require one type of testing over another. This clear signal would move product development forward by bringing written policy up to date with stated policy and science, and by paving the way for industry to develop and use emerging, superior technologies. Nearly nine years later, FDA has not provided a substantive response.

Conclusion

We are on the verge of the next phase of modern drug development made possible by powerful innovations. In this regard, the U.S. Congress has a vital role to play through enacting discerning legislation like the FDA Modernization Act 3.0 to make this possible and usher in the new era of human-relevant biomedical discoveries.

The significant value of this legislation to the public and patients in the Rare Disease community comes in the form of reducing the failure rate in translating scientific findings from the lab to the clinic. That includes not mislabeling a toxic or ineffective drug as safe or effective, not mislabeling

[11] Asterand Bioscience, AxoSim, Empiriko, Friends of Cancer Research, Hurel Corp, In Vitro ADMET Laboratories, Invitro Cue, InVitro International, MatTek Corporation, National Organization for Rare Disorders, Safer Medicines Trust, United Spinal Association, 3D Biomatrix, Inc.)

a safe or effective drug as harmful or ineffective, and not enabling human-irrelevant models to continue to be the paradigm for our national drug discovery process and the development of modern medicines, especially in the presence of technology-driven alternatives. Decades of animal testing proved to be misleading, distracting, and utterly unwise investments.

We hope that the committee will favorably report H.R. 7248 with amendments agreed upon by the bill's authors.

Respectfully,

Wayne Pacelle is President of Animal Wellness Action and the Center for a Humane Economy.

Tamara Drake is Director of Research and Regulatory Policy for the Center for a Humane Economy

Zaher Nahle, PhD MPA is the Senior Scientific Advisor for Animal Wellness Action and the Center for a Humane Economy

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The FDA Modernization Act 3.0

(H.R. 7248)

The FDA Modernization Act 2.0 (FDAMA 2.0) was enacted into law as Sec. 3209 of the Consolidated Appropriations Act, 2023, which President Biden signed on Dec. 29, 2022. FDAMA 2.0 lifted a mandate in the Federal Food, Drug, and Cosmetic Act (FDCA) that required animal testing of investigational new drugs (INDs) to establish safety and efficacy prior to clinical trials in humans.

FDAMA 2.0 did not ban animal testing, but it offered drug sponsors the option to use 21st century alternatives such as cell-based assays, organ chips, computer modeling, and bioprinting. The goal was not only to make drug testing more humane, speed drug development by reducing the attrition rate, since non-animal methods are typically superior predictors of human responses to drugs. An astonishing 90-95% of drugs that pass animal tests go on to fail in human clinical trials, wasting precious time for patients.

Over 7,000 rare diseases affect between 25-35 million Americans—and 95% of those diseases have no cure. Rare-disease patients stand to benefit substantially by the acceptance of non-animal methods because the poor reliability of animal models compounds high R&D costs to disincentivize investment in this area. The innovative 21st century methods outlined in FDAMA 2.0 are among the most promising frontiers in understanding rare diseases: organ chips for Barth Syndrome, 3D models (organoids) of the midbrain for NGLY1 deficiency (a rare neurological disease), and artificial intelligence (AI) in developing treatments for Fragile-X syndrome. As a 2022 article noted of Fragile-X, "[t]his is a disease for which there were no mouse models. A different approach was needed, and the patients-on-a-chip model, combined with AI, seemed to be the best solution."

The Problem

To date, the FDA has not updated its regulations to conform with the law Congress passed in 2022. Dozens of FDA regulations continue to call for animal tests without offering drug sponsors any other option. FDA programs that qualify non-animal test methods are cursory, ineffective, and lack transparency.

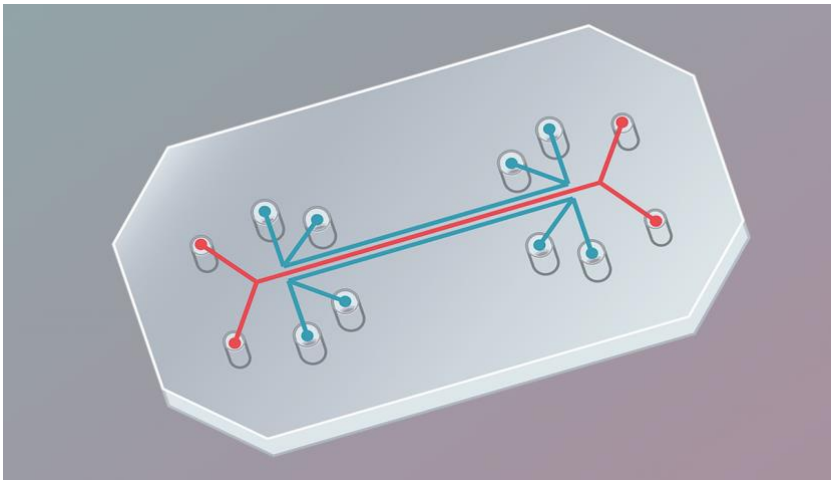
The Solution

To effectuate the will of Congress, the FDA Modernization Act 3.0 would:

- Require the FDA to publish a final rule to fully implement FDAMA 2.0.
- Require the HHS Secretary to establish a process to qualify test methods to reduce or

replace animal tests. The new methods must either 1) improve test predictivity for safety and efficacy or 2) reduce development time for drugs and/or biologics.

- Require the HHS Secretary to hold a public meeting of stakeholders to solicit input about the qualification process for non-animal methods. After this public meeting, the FDA must propose guidance, provide a comment period, and finalize the guidance within a year of comments closing.
- Require the FDA to publish an annual report on its website analyzing the success of the qualification process, including an estimate of the number of animals saved by it.



[1] National Institutes of Health, National Center for Advancing Translational Sciences (NCATS), "New Therapeutic Uses": https://ncats.nih.gov/research/research-activities/ntu. Accessed 28 Jan. 2024. Additionally, federal regulations already recognize that "animal reproduction studies are not always predictive of human response." *See* 21 C.F.R. §201.80(f)(6)(i)(b).

[1] Ed Miseta, "Needed: An AI Revolution in the Rare Disease Space," *Clinical Leader*, 11 Nov. 2022: https://www.clinicalleader.com/doc/needed-an-ai-revolution-in-the-rare-disease-space-0001

[1] *See* 21 C.F.R. §§ 312.22(c), 312.23(a)(3)(iv), 312.23(a)(5)(ii), 312.23(a)(5)(iii), 312.23(a)(8), 312.23(a)(8)(i), 312.23(a)(8)(ii), 312.23(a)(10)(i), 312.23(a)(10)(ii), 312.33(a)(6), 312.82(a), 312.88, 312.160, 314.50(d)(2), 314.50(d)(2)(iv), 314.50(d)(5)(i), 314.50(d)(5)(vi)(a), 314.50(d)(5)(vi)(b), 314.93(e)(2), 315.6(d), 330.10(a)(2), 610.35(d), 812.2(c), 812.5(c), 812.27(a), 812.35(a)(3)(iii), 860.5(f), and 860.7(d)(2). For uniformity and consistency, the following regulations should also be updated: 21 C.F.R. §§ 3.7, 10.20, 14.95, 16.1, 50.24, 58.3, 201.56, 201.57, 201.1, 312.32, 312.160, 314.81, 314.200, 314.430, 316.20, 330.14, 343.80, and 361.1. Definitions sections in the following regulations also must be harmonized with Sec. 3209 of the *Consolidated Appropriations Act, 2023*, P.L. 117-328, 136 Stat. 5822 (2022): 21 C.F.R. §§ 310.3, 312.3, 314.3, 315.2, 601.31, 812.3, and 860.3.

United States Senate
WASHINGTON, DC 20510

16 November 2023

Robert M. Califf, M.D.
Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Dear Dr. Califf:

We write to you about the investigational new drug development work of the FDA in the wake of the enactment of the FDA Modernization Act 2.0.

That legislation, which Congress passed and the President signed into law at the end of 2022 with uncommon unanimity, removes FDA's mandate for animal testing of all new drug candidates and allows an applicant for new drug market approval to use methods other than animal testing to establish a drug's safety and effectiveness. During one of your appearances before the U.S. Senate Committee on Health, Education, Labor, and Pensions, you spoke favorably about the shift toward human-based biology, noting that alternative methods may include cell-based assays, organ chips and micro-physiological systems, computer modeling, bioprinting, and a growing variety of other New Approach Methodologies (NAMs).

As you are aware, agency regulations are promulgated in accordance and conformity with Congress's statutory language and intent. Yet in the aftermath of the enactment of the FDA Modernization Act 2.0, the FDA's regulations related to animal testing no longer fully conform with applicable law. For example, federal regulations governing submission of Investigational New Drug (IND) applications require that amendments to an IND "should be supported by additional information, including the results of animal toxicology studies or other human studies as appropriate."[1] Further, regulations governing the IND Investigator's Brochure call for a summary of "pharmacological and toxicological effects of the drug in animals and, to the extent known, in humans."[2] These and other regulatory provisions no longer reflect the full scope of the governing statute and should therefore be updated as expeditiously as possible.

The above examples are just a sampling of a larger set of inconsistencies between the amended statute and FDA regulations. We therefore write to ask what specific steps the FDA is taking to update its animal testing regulations, and what its timeline is for implementation of a revised regulatory framework. Please respond with this information within 30 days of the date of this letter.

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[1] *See* 21 C.F.R. § 312.22(c).

[2] *See* 21 C.F.R. 312.23(a)(5)(ii).

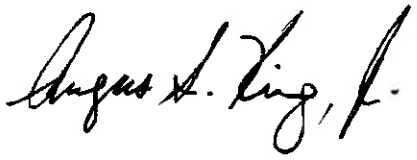
Thank you for your attention to this important matter.

Sincerely,

Rand Paul, M.D.
United States Senator

Cory Booker
United States Senator

Mike Braun
United States Senator



Angus King
United States Senator

Roger Marshall, M.D.
United States Senator

Tim Kaine
United States Senator

John Kennedy
United States Senator

Ben Ray Luján
United States Senator

Eric S. Schmitt
United States Senator

Exhibit A Regulation Updates

To conform with the updates to the Federal Food Drug and Cosmetics Act, the following regulatory text must be issued and placed under the definition sections of 21 C.F.R. §§ 310.3, 312.3, 314.3, 315.2, 601.31, 812.3, 860.3:

Nonclinical test defined
"Nonclinical test" means a test conducted in vitro, in silico, or in chemico, or a nonhuman in vivo test, that occurs before or during the clinical trial phase of the investigation of the safety and effectiveness of a drug. Such test may include the following:

(1) Cell-based assays.
(2) Organ chips and microphysiological systems.
(3) Computer modeling.
(4) Other nonhuman or human biology-based test methods, such as bioprinting.
(5) Animal tests.

1. 21 C.F.R. § 312.22(c) (General Principles for IND Submissions)

Proposed: *The central focus of the initial IND submission should be on the general investigational plan and the protocols for specific human studies. Subsequent amendments to the IND that contain new or revised protocols should build logically on previous submissions and should be supported by additional information, including the results of ~~animal~~ nonclinical toxicology studies or other human studies as appropriate. . . .*

2. 21 C.F.R. § 312.23(a)(3)(iv) ((IND Content and Format)

Proposed: *A brief description of the overall plan for investigating the drug product for the following year. The plan should include . . . . (f) any risks of particular severity or seriousness anticipated on the basis of the toxicological data ~~in animals~~ from nonclinical or prior studies in humans with the drug or related drugs.*

3. 21 C.F.R. § 312.23(a)(5)(ii) (IND Investigator's Brochure)

Proposed: *A summary of the pharmacological and toxicological effects of the drug in ~~animals~~ nonclinical tests and, to the extent known, in humans.*

4. 21 C.F.R. § 312.23(a)(5)(iii) (Investigator's Brochure)

Proposed: *A summary of the pharmacokinetics and biological disposition of the drug in ~~animals~~ nonclinical tests and, if known, in humans.*

5. 21 C.F.R. § 312.23(a)(8) (IND Pharmacology and Toxicology Information)

Proposed: *Pharmacology and toxicology information. Adequate information about pharmacological and toxicological studies of the drug involving ~~laboratory animals or in vitro~~ nonclinical tests, on the basis of which the sponsor has concluded that it is reasonably safe to*

conduct the proposed clinical investigations. The kind, duration, and scope of ~~animal and other tests~~ nonclinical tests required varies with the duration and nature of the proposed clinical investigations. . . .

6. 21 C.F.R. § 312.23(a)(8)(i) (Pharmacology and Drug Disposition)

Proposed: *Pharmacology and drug disposition. A section describing the pharmacological effects and mechanism(s) of action of the drug in ~~animals~~ nonclinical tests, and information on the absorption, distribution, metabolism, and excretion of the drug, if known.*

7. 21 C.F.R. § 312.23(a)(8)(ii) (Toxicology)

Proposed: *Toxicology. (a) An integrated summary of the toxicological effects of the drug in ~~animals and in vitro~~ nonclinical tests. Depending on the nature of the drug and the phase of the investigation, the description is to include the results of acute, subacute, and chronic toxicity tests; ~~preclinical~~ tests of the drug's effects on reproduction and the developing fetus; any special toxicity test related to the drug's particular mode of administration or conditions of use (e.g., inhalation, dermal, or ocular toxicology); and any in vitro studies intended to evaluate drug toxicity.*

8. 21 C.F.R. § 312.23(a)(10)(i) (Drug Dependence and Abuse Potential)

Proposed: *Drug dependence and abuse potential. If the drug is a psychotropic substance or otherwise has abuse potential, a section describing relevant clinical studies and experience and studies in ~~test animals~~ nonclinical tests.*

9. 21 C.F.R. § 312.23(a)(10)(ii) (Radioactive Drugs)

Proposed: *Radioactive drugs. If the drug is a radioactive drug, sufficient data from ~~animal~~ nonclinical or human studies to allow a reasonable calculation of radiation-absorbed dose to the whole body and critical organs upon administration to a human subject. . . .*

10. 21 C.F.R. § 312.33(a)(6) (Content of Annual Reports)

Proposed: *A list of the ~~preclinical~~ nonclinical studies ~~(including animal studies)~~ completed or in progress during the past year and a summary of the major ~~preclinical~~ nonclinical findings.*

11. 21 C.F.R. § 312.82(a) (Early Consultation)

Proposed: *Pre-investigational new drug (IND) meetings. Prior to the submission of the initial IND, the sponsor may request a meeting with FDA-reviewing officials. The primary purpose of this meeting is to review and reach agreement on the design of ~~animal~~ nonclinical studies needed to initiate human testing. . . .*

12. 21 C.F.R. § 312.88 (Safeguards for Patient Safety)

Proposed: *All of the safeguards incorporated within Parts 50, 56, 312, 314, and 600 of this chapter designed to ensure the safety of clinical testing and the safety of products following marketing approval apply to drugs covered by this section. . . . These safeguards further include the review of ~~animal~~ nonclinical studies prior to initial human testing (¤ 312.23) . . . .*

13. 21 C.F.R. § 312.160 (Drugs for Investigational Use in ~~Laboratory Research Animals on In Vitro Tests~~ in Nonclinical Tests).

Proposed: *Drugs for investigational use in ~~laboratory research animals or in vitro~~ nonclinical tests. . . . A person may ship a drug intended solely for ~~tests in vitro or in animals used only for laboratory research purposes~~ nonclinical tests if it is labeled as follows:*
CAUTION: Contains a new drug for investigational use only in ~~laboratory research animals or for tests in vitro~~ nonclinical tests.. Not for use in humans. . . . (2) A person shipping a drug under paragraph (a) of this section shall use due diligence to assure that the consignee is regularly engaged in conducting such tests and that the shipment of the new drug will actually be used for nonclinical testing ~~tests in vitro or in animals used only for laboratory research.~~

14. 21 C.F.R. § 314.50(d)(2) (NDA Technical Sections)

Proposed: *Nonclinical pharmacology and toxicology section. A section describing, with the aid of graphs and tables, ~~animal and in vitro~~ nonclinical studies with drug . . . .*

15. 21 C.F.R. § 314.50(d)(2)(iv) (NDA Non-Clinical Sections)

Proposed: *Any nonclinical studies of the absorption, distribution, metabolism, and excretion of the drug ~~in animals~~.*

16. 21 C.F.R. § 314.50(d)(5)(i) (Clinical Data Section)

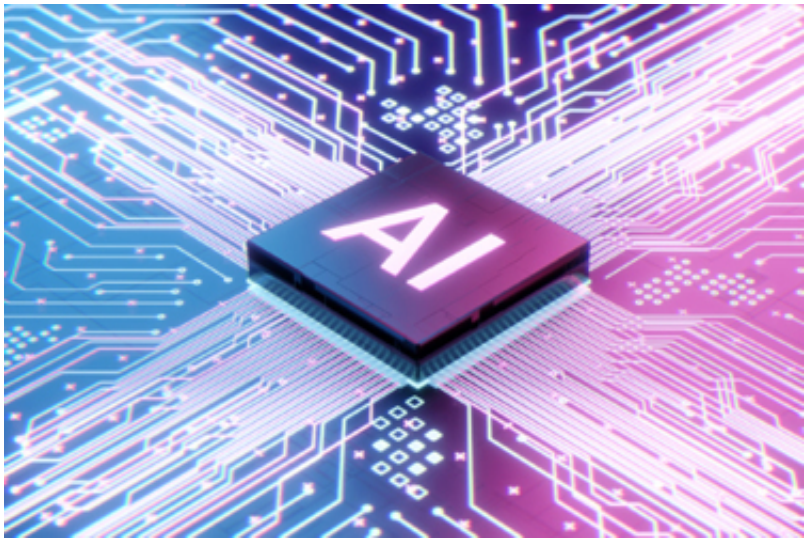
Proposed: *A description and analysis of each clinical pharmacology study of the drug, including a brief comparison of the results of the human studies with the ~~animal~~ nonclinical pharmacology and toxicology data.*

17. 21 C.F.R. § 314.50(d)(5)(vi)(a) (Clinical Data Section)

Proposed: *(a) The applicant shall submit an integrated summary of all available information about the safety of the drug product, including pertinent ~~animal~~ nonclinical data, demonstrated or potential adverse effects of the drug, clinically significant drug/drug interactions, and other safety considerations . . . .*

Needed: An AI Revolution In The Rare Disease Space

By Ed Miseta, Chief Editor, Clinical Leader



Quris is involved in the rare disease space. The company has developed a treatment for Fragile-X Syndrome, the most common inherited cause of autism and intellectual disabilities worldwide. Isaac Bentwich M.D., the founder and CEO of Quris, believes the rare disease space, in general, is a difficult one to navigate. Fragile-X Syndrome itself has many challenges, and he notes Novartis and Roche have both failed in attempts to develop a drug for it. Bentwich believes the biggest challenge companies face is financial.

"Right now, the tools available to pharma, and the approach they use, make it exceedingly difficult, if not impossible, to develop rare disease drugs," he says. "The economics of drug development tell a good part of the story. It costs $2.5 billion and 12 to 18 years, on average, to develop a new drug. In the rare disease space, where there is a smaller number of patients, those numbers are simply unsustainable."

Bentwich notes there are many rare diseases and a patient population of 300 million worldwide, but the cost of developing a treatment for any *single* rare disease is what is not financially sustainable. Sadly, even when a drug in development fails to gain regulatory approval, there is still an average cost of $1 billion to the sponsor company. That means any drug gaining approval must generate enough revenue to pay for all the failures as well.

"One of the biggest challenges faced by the industry is knowing which drugs will be successful in human beings and clinical trials," states Bentwich. "If a company experiences 5 or 10 failures before developing a successful drug, the cost of those failures drives the cost of drug development even higher. If the industry had the ability to take only successful drugs through the drug development and clinical testing process, development costs could be reduced."

An Economic Conundrum

To better illustrate the conundrum, Bentwich uses a real estate example. If you wanted a skyscraper, you would find an architect to build it for you. Suppose that architect agrees to build 10 skyscrapers that you must pay for, and nine of the buildings are guaranteed to collapse. Your challenge would be to collect enough rent on the 10th building to pay for the cost of that building and the nine others. Alternatively, if you knew which building would not collapse, you could simply have that one built and skip the others. Bentwich believes the current economics in the drug development space are similar. It is simply untenable for pharma to keep spending money to develop drugs that will fail. Companies need to determine which of 10 potential treatments will be safe and effective in humans.

"This conundrum is one of the reasons why pharma companies will gravitate towards blockbuster drugs," he says. "It is the easiest way for them to cover

the costs of drug development. It is also the reason many companies prefer to avoid the rare disease and ultra-rare disease space altogether."

There are several reasons why a new drug might fail in clinical trials. One of the biggest issues faced by the industry is animal testing, which Bentwich notes does not accurately predict the safety of a drug in humans. He points to the FDA Modernization Act recently approved by unanimous vote by Senate, and now on its way to be signed into law, expected before year-end, as acknowledgement that animal studies are not a good predictor of success in humans. The Act will remove the requirement for sponsor companies to evaluate treatments on animals before administering them to humans.

In the rare disease space, there are not a lot of patients. This results in many studies being more expensive global trials. For many rare diseases, researchers also do not have access to a natural history of the disease. Combine those factors together, and you have a situation that is more difficult than the challenges faced in other therapeutic areas. Bentwich believes the solution to this problem is artificial intelligence (AI).

AI Can Determine Winners

Ideally, we would want to know, before a trial begins, if a treatment will be safe and effective in humans. In addition to the expense, Bentwich believes it is inhumane to put patients through a trial for a treatment that will not gain regulatory approval. AI is a technology that can help researchers determine which molecules are likely to end in failure. To illustrate, Bentwich gives the following example.

"If you wanted to create an AI machine that discerns cats from dogs, how would you go about it?" he asks. "You can take 500 cats and 500 dogs and run them through a scan that looks at different properties of these animals. The scan could look at the fur, tail, head, teeth, and paws of a group of

animals. You scan 500 cats and look at those factors, and then scan 500 dogs and look at the same factors. By the time animal number 1001 is scanned, the AI will be able to tell you whether it is a dog or a cat."

A technology known as Bio-AI uses patients-on-a-chip, which allows researchers to view miniaturized human tissues and organs on small chips that are less than a millimeter in size. Those researchers can then apply known drugs to those chips, rather than evaluating them on mice, and train the AI to recognize the difference. That is the essence of what Quris is trying to do.

"We are combining three disciplines: patients-on-a-chip, stem cell genomic diversity, and AI," says Bentwich. "This will allow us to determine which drugs will be safe in the human body. We can run the test on many different patients on a chip and train the AI, like the dog/cat example. If we show the AI 500 drugs that are safe in humans and 500 drugs that are not, when we show it drug number 1001, the AI will be able to tell us if that drug will be safe in humans."

Quris was able to look at 1,036 drugs that FDA has classified over the years by their level of toxicity to the liver. These drugs went through invitro testing, animal testing, and clinical trials and seemed fine, yet some were still found to be toxic in humans.

"Those 1,036 drugs are our dogs and cats," says Bentwich. "We know which are toxic and which are not. We run them on our platform, all the mini patients-on-a-chip, and let the AI study them. When an unknown drug comes along, we run it through the same platform and ask if it looks more like the toxic drugs or the non-toxic ones. We believe this approach will be the next generation of addressing rare disease drug development."

A New Solution Is Needed

Although Quris started out as a drug development company, Bentwich notes he was intrigued about how drugs are developed, especially in the rare disease space. The conundrum in that space became clear to him and he knew there had to be a better way of determining which treatments would be safe in humans. That problem led to the development of a technology solution.

The platform the company is using was developed entirely inhouse, and one that he says was developed out of necessity. He uses the company's development of Fragile-X as an example. This is a disease for which there were no mouse models. A different approach was needed, and the patients-on-a-chip model, combined with AI, seemed to be the best solution.

The AI expertise needed already existed inhouse. Bentwich is a medical doctor by training but has spent many years working on AI and other technology solutions for the life sciences industry. To develop the capabilities, Quris brought in technology experts from different domains including miniaturized biology engineering and machine learning to develop this capability.

Other pharma companies may also be interested in using the technology to predict the success or failure of their own drugs. Bentwich notes Quris will make it available to other pharma and biotech firms to maximize the impact of the technology. "We will make it available to any companies that have an interest," he adds. "We believe the impact of this technology will be felt around the wo

iXCells Biotechnologies Announces Grand Opening and 2024 Rare Disease Month Workshop

Thu, Feb 1, 2024

New 30,000 SF San Diego, California facility adds substantial capacity to sustain future growth.

SAN DIEGO, February 01, 2024--(BUSINESS WIRE)--iXCells Biotechnologies USA, Inc. ("iXCells"), a cell technology company providing innovative cell products and preclinical drug development services to the global academic, biotech, pharmaceutical, and rare disease communities today announced the grand opening celebration of its new San Diego headquarters and Rare Disease Month Workshop.

A ribbon-cutting ceremony scheduled February 8th at 9am marks a milestone in the company's growth, the grand opening of its new facility located at 10100 Willow Creek Road. This special event will be attended by invited guests, employees, leading industry scientists, entrepreneurs from the rare disease community, and San Diego's honorable Mayor, Todd Gloria.

The company's new 30,000 SF facility supports increasing market demand for disease relevant cell-based models and assay systems, such as iPSC derived cells, primary cells, 2 and 3-D cell culture models, organoids, and AI-ML based approaches. The pharmaceutical industry is increasingly shifting away from in-vivo animal models towards alternative cell-based systems since the FDA Modernization Act 2.0 signed into law December 29, 2022, now allows

organizations to submit non-animal data using such alternative technologies to demonstrate the safety and efficacy of investigational drugs prior to conducting clinical trials.

iXCells Biotechnologies continues to play a leadership role in providing CRO services and fostering industry collaboration and innovation to support the rare disease community, spearheaded by its Co-Founder and President, Dr. Nianwei Lin. A rare disease is described as a life-threatening or chronically debilitating disease having low prevalence and is often genetically predisposed - for example, a disease affecting less than 200,000 people in U.S, fewer than 2,000 people in EU, and according to World Health Organization, fewer than 65 per 100,000. Currently there are more than 10,000 distinct types of rare genetic diseases, affecting 20 million people in the US and 400 million globally. Among these patients, 50% of them are children, and many of them won't live to see their 5^{th} birthday. Ninety five percent (95%) of rare diseases lack an FDA approved treatment.

This year's Rare Disease Workshop will include talks from rare disease patient foundation leaders, scientific presentations covering iPSC derived CNS models, antisense oligonucleotide (ASO) development, industry collaborations in the Nof1 ecosystem, roundtable discussions and networking.

The company's newly appointed CEO, Dr. Helge Bastian, said, "We're thrilled to be officially celebrating this important milestone with our valued customers and employees, industry leaders, Great Point Partners, and Mayor Gloria. iXCells is a shining example of what an organization can accomplish with dedicated employees and a fervent desire to provide innovative solutions to some of the industry's most challenging aspects of preclinical development."

San Diego Mayor, Todd Gloria, commented, "San Diego's life-sciences companies are on the vanguard of drug research and development. iXCells Biotechnologies' pursuit of groundbreaking scientific advancements toward cures for common, rare, and ultra-rare diseases is truly remarkable, and I am delighted to support the important work they do both locally and worldwide."

About iXCells Biotechnologies

Founded in 2014 and based in San Diego, CA, iXCells Biotechnologies is an innovative cell biology and cell technology company dedicated to providing preclinical drug discovery solutions with the focus on disease relevant cellular models enabling technologies and services to the academic, biotech and pharma communities to accelerate the pace of drug discovery. iXCells offers customers access to high quality primary and iPSC derived cells, custom iPSC services, functional bioassay development and drug

screening. To learn more about this innovative leader within the preclinical iPSC sector, visit .

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