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Passage of FDA Modernization Act 2.0 Opens Opportunities for New Alternative Methods in Drug Development

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Medical research has relied on model organisms to study human biology, diseases, and therapeutics. Such model organisms can include, but are not limited to, fruit flies, zebrafish, rodents, and non-human primates. The use of model organisms has revolutionized our understanding of innumerable diseases and has contributed to novel therapeutic developments; however, concerns regarding translatability, ethics, and scarcity are a few of several drivers that led to the passage of the FDA Modernization Act 2.0. The bill is intended to replace, reduce, and refine the use of lab animals for more accurate, precise, and faster drug development. This is a positive step forward for the life sciences ecosystem with broad implications.

Until recently, FDA required preclinical studies on two mammalian species as a part of its investigational new drug (IND) application to assess drug's pharmacology and toxicology. However, model organisms are not always predictive for immunogenicity and other toxicities in humans. FDA also does not always require *in vivo* animal efficacy testing as a part of the IND application. In fact, 80 to 90% of preclinical drug candidates have historically failed, largely driven by the lack of clinical efficacy and/or safety concerns[1,2]. Advancements of these New Alternative Methods (NAMs) may be as good or possibly better than existing approaches and may ultimately reduce substantially or even replace the use of lab animals in preclinical testing. Passage of this bill may also, over time, mitigate some of the high failure rates through the combination of traditional approaches and NAMs to improve predictive ability for risk and efficacy.

Translatability of model organisms to humans is a major bottleneck to drug development. Scientifically and pathologically relevant model organisms are required to understand pathobiology and to evaluate therapeutic efficacy. ImCheck, one of Agent Capital's portfolio companies, has faced a particularly difficult hurdle: the absence of a representative model. ImCheck is developing immunotherapeutic antibodies targeting butyrophilin 3A that engages $\gamma\delta$ T cells, specifically the $\gamma 9\delta 2$ T cells. However, as stated by Pierre d'Epenoux, CEO of ImCheck, "there is no butyrophilin 3A in any rodent species and neither do they have $V\gamma 9V\delta 2$ T cells, which limited our use of available cancer models… We've only been able to rely on animal models for safety testing and focused on *in vitro* / *ex vivo human cell models* to demonstrate our cancer killing effects."

ImCheck's lead program has begun showing early signs of efficacy in their EVICTION, phase I/II clinical trial. Although ImCheck successfully reached the clinic with its lead program, the example highlights that such products for some patients may not be developed or would take enormous amounts of wasted resources if we had to solely rely on and create genetically-modified animal models to try to mimic human biology. Passage of the FDA Modernization Act 2.0 may allow ImCheck to continue exploring New Alternative Methods (NAMs), including *in silico* and *in vitro* studies with human tissues, artificial intelligence, machine learning, and electronic health records studies in place of traditional preclinical animal models and advance such exciting science for patient needs.

Reducing the use of lab animals with NAMs will likely have significant influences on the timeline of drug development. While the time it takes for a drug to be tested and approved can vary, time is often a constraint. Unlike *in vivo* animal testing, NAMs provide a faster throughput and time to result, which has the potential to significantly accelerate the therapeutic development timeline.

Amanda Wagner, CEO of Immunitas – Agent Capital portfolio company, is also in favor of the FDA Modernization Act 2.0. “Obviously there are some circumstances where we have not identified strong NAMs so far, but this presents an opportunity to break new ground. Whenever it is reasonable and feasible to reduce animal safety testing, we should absolutely do so.”

Immunitas’ approach relies on human tumor samples and primary cells to start with and stay closer to the most relevant and translatable biology. “For many therapeutics there aren’t good animal surrogates,” Wagner said. “When possible, we should embrace human biology and prior experience to predict safety and tolerability. In the long run, NAMs may accelerate timelines and increase efficiency.”

As a part of FDA’s initiative to advance alternative methods, CN Bio, a leading organ-on-a-chip (OOC) company that designs and manufactures single- and multi-organ microphysiological systems (MPS), announced on January 17, 2023 that they are expanding collaboration with the FDA to evaluate their multiorgan MPS (link to their press release here)[3].

With the mandate on animal testing lifted, the question now becomes how quickly will we shift towards NAMs and to what extent? Our Agent Capital Venture Partner, John Orloff, believes that it will take some time for that shift to happen. “The biggest hurdle is the mindset and the trust in the new techniques from the industry side and also from the FDA side… Initially, it may be used as a complement to reduce animal testing. As we gain additional experience and trust in the methods, and the information derived from these [NAMs] is shown to have potential advantages over animal testing, such as greater translatability … we could completely supplant animal testing altogether in the future, but that’s not going to happen overnight.”

There is a continued need to improve the quality of preclinical results in a safe manner. Agent Capital supports the FDA Modernization Act 2.0 to advance new alternative methods that may ultimately improve success rates of clinical trials and reduce the reliance on animal testing. We are excited about its implications for the biotech ecosystem and the future of drug development.

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