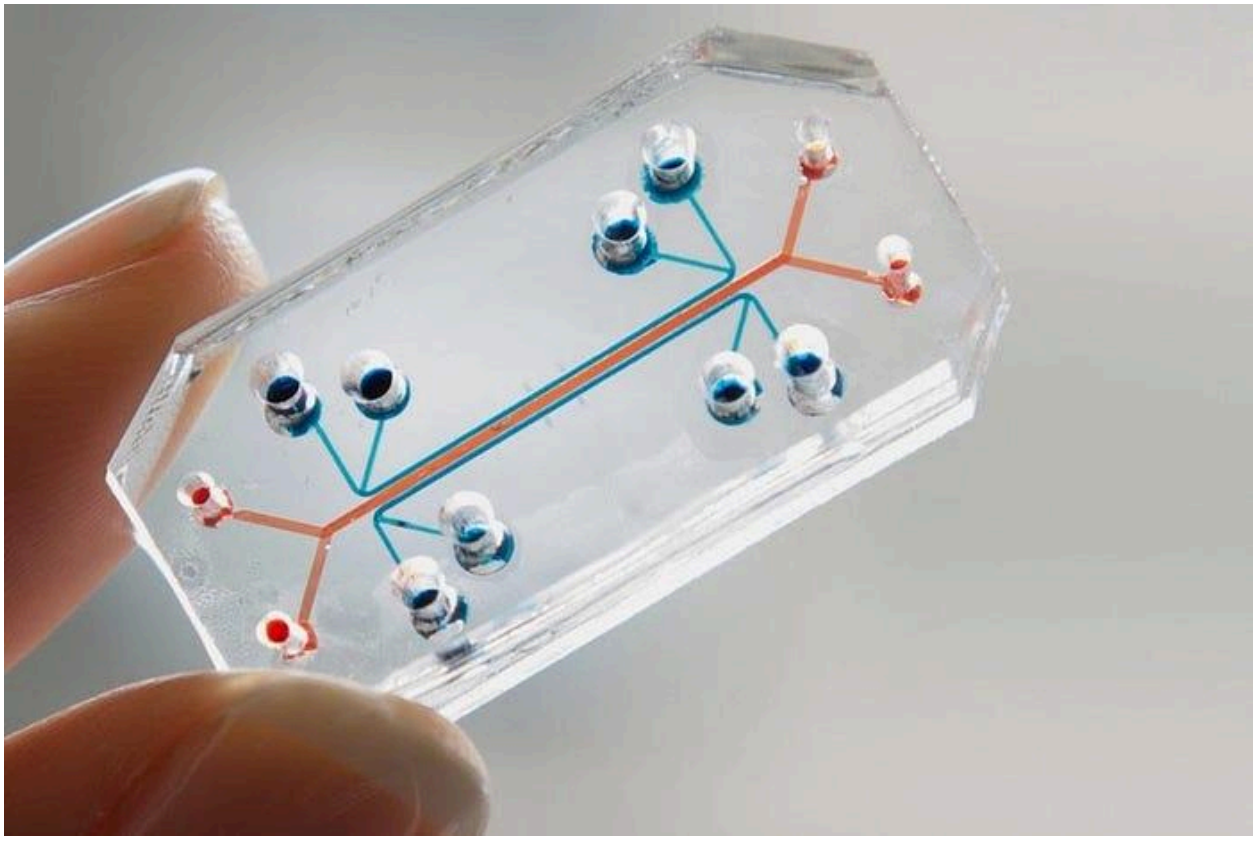
Source: Organs-on-Chip, Review on The Technology, and How the FDA is working with multiple verticals! | Medium



HARSHITHA GOVINDARAJU

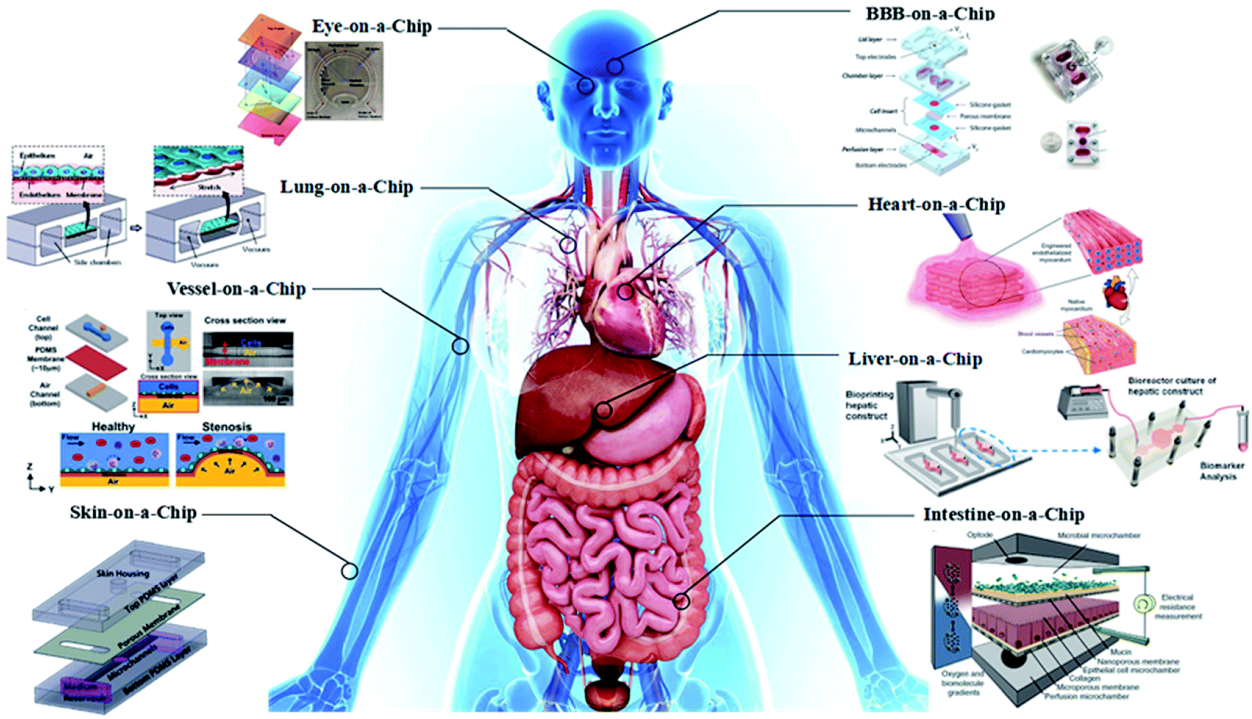
Introduction

Organs on Chips (OOCs) are microdevices that can emulate the functional units of living organs to remodel pathophysiology of human organs in-vitro. These devices can then be used for testing and analysis of drugs and their reactions to the human body. These microsystems are potentially capable of replacing conventional animal models for pharmaceutical, chemical, and environmental applications. They are ideally microfluidic chips that are lined with living cells and the fabrication methods can be configured and designed to mimic the lungs, liver, intestine, and brain. Notable advantages with this ingenious device are its size, the chip's transparency to understand clearly the response at cellular and molecular level, flexibility in configurations, and comparatively easier disposal.



Source: Wyss Institute of Technology

The organ-chips are then integrated onto a complex modular instrument to conduct further research and studies. In addition to this, various organ-chips can be interconnected to observe responses at different organ levels. The data obtained from the experimentation with this system can be then evaluated using advanced analytical tools to obtain accurate results. Combined with this is a software that is designed to help control the system.



Overview of Organ-on-chip Technology[27]

In my opinion, this revolutionary technology plays an important role at various levels and can effectively change the methodologies in studying the bacterial pathogenicity in foods, the effects of drugs, and other detrimental substances to the human body.

More importantly, when an experimental process involving lab animals fails, disposal of it feels inhumane but in the case of these microdevices, disposal is easier, less harmful to the ecology, and meets the ethical concerns.[2] Even though this technology is dated back to the 1980s, it was not until recent years that efforts have been made to begin commercialization.

Research Investigations and Collaborations

Acute Radiation Syndrome(ARS) is an ailment that affects the human body/organs from high amounts of exposure to radiation in a short period.[4] Iconic cases for people who were exposed to these

radiations were from the incidents of Hiroshima and Nagasaki atomic bombs, and the firefighters that first responded after the Chernobyl Nuclear Power Plant event in 1986. Daily a lot of the human population is at risk from such exposure including workers/clinicians in labs containing highly radioactive sources, power plants, military soldiers a.k.a atomic veterans, etc. Consequently, 3 classic syndromes are observed when exposed: Bone Marrow Syndrome, Gastrointestinal (GI) Syndrome, Cardiovascular (CV)/ Central Nervous System (CNS) Syndrome. A complex number of degrading changes are seen in the human body after it is exposed to such radiation at an organ, cellular, and molecular level.[5] In addition to this, animal models cannot mimic certain radiation responses that are specific to humans.

This was a concerning issue to the FDA and to address the above challenges[6], they collaborated with Harvard University's Wyss Institute for Biologically Inspired Engineering. The project's principal investigator is Dr. Donald E Ingber, MD, Ph.D., awarded with an initial contract value of $5,625,079 and an additional follow on study value of $398,000. The intensive research lasted from September 2013 to April 2019. It focused on coming up with methodologies to test candidate exposure to radiation and nuclear energies and provide medical countermeasures.[3] The institute developed organ-on-chips to model the radiation damage in lung, gut, and bone marrow and then make use of these models to test the candidate's medical countermeasures. The three chips are primarily studied as these organ systems are more prone to toxic radiation effects. Lungs, because the airborne particles can be directly inhaled. Gut and bone marrow, because they are known to have high cell turnover rates and they are known to promote cancerous growth along with protection against aging.

Source: Wyss Institute

Another interesting update about this initiative was that FDA's Medical Countermeasures Initiative (MCMi), at FDA's Office of the Chief Scientist and FDA's Office of Women's Health (OWH), within the Office of the Commissioner, collaborated to fund this research additionally, which will help the

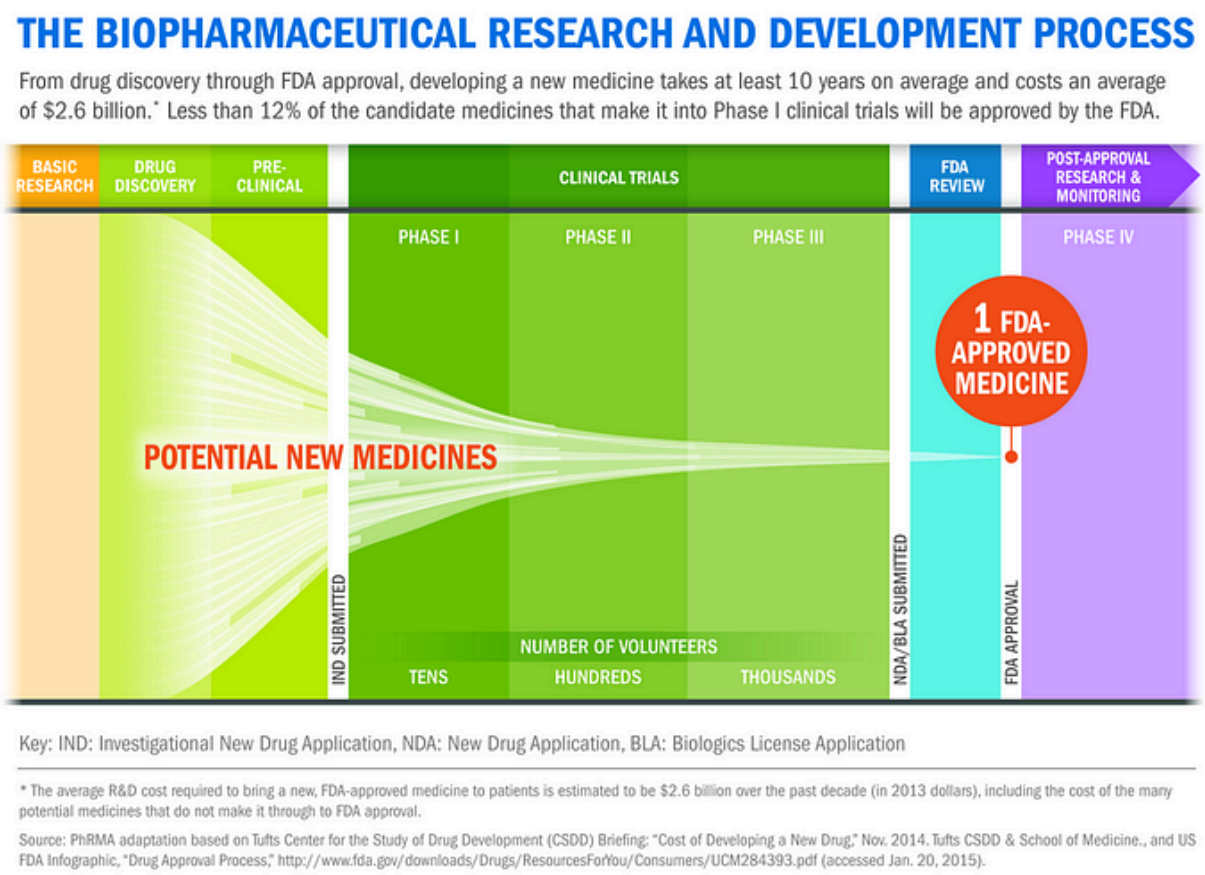
scientific community better understand how sex differences impact the body's response to MCMs for radiological and nuclear preparedness.[6]

It was proven that the Bone marrow chip could successfully produce human red and white blood cells and mimic responses to ionizing radiation as well as effects of known chemotherapies and radiation countermeasure drugs.[7]

But why sex difference studies? They were also successful in answering these questions through the current technology in question: organ-on-chip

Currently, the institute has now successfully produced and tested around 10 organ-on-chips on this particular research.[8] They used a human Gut-on-a-Chip (Gut-Chip) microfluidic device lined by human intestinal epithelial cells and vascular endothelial cells to model radiation injury and assess the efficacy of radiation countermeasure drugs in-vitro. Using a bone marrow-on-a-chip microfluidic device, the team was able to culture living hematopoietic bone marrow. This was then observed to mimic radiation toxicity in-vitro. Later they used this microdevice to demonstrate continuous blood cell production in-vitro and model bone-marrow responses to potential radiation countermeasure drugs. They tested for 2 potential therapeutics- 1)Granulocyte-colony stimulating factor and 2)Bactericidal/permeability-increasing protein (BPI), both induced significant increases in the number of hematopoietic stem cells and myeloid cells in the fluidic outflow. They compared the study with a static marrow culture and results were not seen in the latter even though they were previously proven to cause accelerated recovery from radiation-exposed toxicity.[9]

The FDA approval process involves pre-clinical and clinical studies. It is a known fact that some drugs take about 10 years to come to market from the date of its discovery.



Source: FDA

In the overview diagram of the drug development process, we can observe how the curve degrades from one step to another in the processes throughout the pre-clinical and clinical trial studies and how arduous and extortionate it can get. The current estimates show only 13.8% of the drugs that are tested attain clinical success and lead its way for the FDA approval. And about 1/10 drugs make it to the market successfully. Organ-on-chips was able to address all these gridlocks and animal ethical concerns.[10]

To characterize a drug, its “pharmacokinetics” (PK) and “pharmacodynamics” (PD) analysis are most important. PK involves the quantification of its absorption, distribution, metabolism, and excretion, together with determining the drug levels in blood and PD gives the effects that the drug produces on

its target organs. Currently, animal models are used for preclinical studies to comprehend PK/PD. Wyss Institute successfully engineered an automated instrument with functional organ-on-chips and computational modeling in combination with experimental data generated which can quantitatively predict human drug PK/PD behavior in-vitro.[11] These experiments and results proved that the devices can ameliorate the current design of drug-administration regimens for phase-I clinical trials.

With enough study-designs and experiments, the institute was successful in launching a start-up to commercialize the product that can create living platforms that can emulate the complexities of human biology to enable unprecedented insights into human biology and health. The company is called EMULATE, Inc. and was founded in 2013.[12] The driving force is to recreate organ-level function to model organs in health and disease states. The technology has applications in pharmaceutical research, product development, testing how different medicines, chemicals, and foods affect human health.

The company has numerous investments and collaborations with NanoDimension, ALS Finding a Cure, Atel Ventures, and Laboratory Corp. of America Holdings, Roche, Takeda, etc. This shows the potential of the product and the research. It has entered into a partnership with the FDA under the Collaborative Research and Development Agreement (CRADA). This arrangement is known to build private companies together with FDA laboratories to develop and nurture the upcoming new technologies to reach the acme of the market. It is known to aid many of the FDA centers including CFAN(Center for Food Safety and Applied Nutrition), CDER(Center for Drug Evaluation and Research), CDRH(Center for Devices and Radiological Health), CBER(Center for Biologics Evaluation and Research).[13] Also, this partnership is said to be focused on the toxicology studies and hence the FDA is mainly interested in the liver chips from species like dogs, rats, and humans.

Companies like MERCK, Johnson and Johnson, COVANCE, NC- based laboratory testing giant LabCorp, AstraZeneca, Cedars-Sinai, University of Southern California, Janssen, SERES Therapeutics, DARPA, Michael J. Fox Foundation and National Center for Advancing Translational Sciences(NIH) have incorporated different products of Emulate's in their studies.[12]

Some noteworthy products include Bio-Kits for testing general toxicity, mechanistic toxicity, drug transport, nutrient metabolism, intestinal absorption, and efficacy testing. Enabled Models to mimic human functionality. Hardware models providing cell -culture modules, microfluidic chip design, and companion products like imaging adapters to help integrate this platform onto the existing lab workflows.[12]

We can understand the potential of this technology to be placed in real-time implementation. The highlight of this platform is to deliver clinically relevant and decision-worthy insights. Around 89% of the drugs that fail in human trials, of which approximately half of those fail due to unanticipated human toxicity[14]. This procurable technology can now make the researchers, pharma companies, etc shift towards these test kits in-turn replacing the animal models.[15]

Tumor-on-chips is another interesting area of research. The 3D-tumor models have similar technology as the organ-on-chips which are microfluidics, imaging, and tissue engineering. The conventional 3D tumor models[16](spheroids and scaffolding) are different from the existing technology that inculcates the microfluidics and is proven to be more efficient in terms of dynamicity. Developing better in-vitro models to understand cancer etiology and its response to anti-cancer drugs can become very challenging. Especially because the complex 3D tissues have extensive chemical signaling within their surrounding environment and are difficult to get to the core of the complex proteomics and metabolomics of cancer. This eventually becomes the reason why less than 10% of the anti-cancer

drugs make it to the market without failing the pre-clinical and clinical development. Anti-cancer pharmaceuticals fail to prove their efficacy and toxicity in human testing.[17]

Another interesting collaboration is with the University of Colorado Denver for Toxicity and Carcinogenicity Profiling of Tobacco Products via Organ Microengineering and Systems Biology. This collaboration was done through the means of research contract and was awarded on September 9th, 2018 under Dr. Erika Clark as the principal investigator. [18]

With the rise in the number of hookah, tobacco smoking, and e-cigarette users; more as a 'trend' in the younger generations, we are seeing a rise in the ill-effects. Apart from creating awareness, it is a key desideratum to invest in research studies related to such intoxicants. This paved the way to develop "Breathing-Smoking Human Lungs-on-a-Chip" to analyze the toxic effects in the above-mentioned users. This study comprises of three phases:

1) Phase I

- Duration of 18 months.

- To develop a 3D human lung-on-a-chip with bioprinting technology.

- To validate its functionality in terms of its physiological responses in-vitro.

2) Phase II

- Duration of 6 months

- To create a smoking robot with different levels and range of exposure to hookah, tobacco, and e-cigarette products.

- To use tubing methodology to pass gases, aerosols, etc with minimal adsorption properties. The software will be used to control the topographies.

3) Phase III

- Duration of 18 months.

- To integrate lung airway with a smoking robot system.

- To conduct organ-level studies and evaluate the effects.

This innovative research will aid in examining pathological responses like oxidative stress, inflammation, matrix remodeling, pH changes, nicotine absorption, and pre-neoplastic transformation at molecular, cellular, tissue, and organ levels. FDA's mission again is to extract this to help them in regulating hookah and e-cigarette products. Upcoming technologies like organs-on-chip will help tighten the process and make the current system more stringent in regulating these products.

Collaboration between the Division of Neurotoxicology(FDA) and the University of Arkansas at Fayetteville(UAF) to develop and validate quantitative biomarkers and discern the biological pathways

that may be linked with the expression of neurotoxicity. Their study-design consisted of 3 systems-Cell-Culture, whole animals, and Humans. Under Cell-Culture they implemented the novel Organ-on-a-chip for modeling of the blood-brain barrier (BBB)-on-a-chip for Traumatic Brain Injury studies(TBI). TBI is a methodology to breakdown the understanding of what exactly happens physically inside the brain.[19] Inferences from the studies showed a higher percentage of stretch-induced cell deaths and how they could control many of the factors in the study when compared to using animal models.

After noting gene alteration in humans who have been to space, various organ-on-chips are now being sent to study various modifications that a human body can face. This NIH funded program can better help understand various phenomena that have been observed over the years w.r.t biological changes.[20]



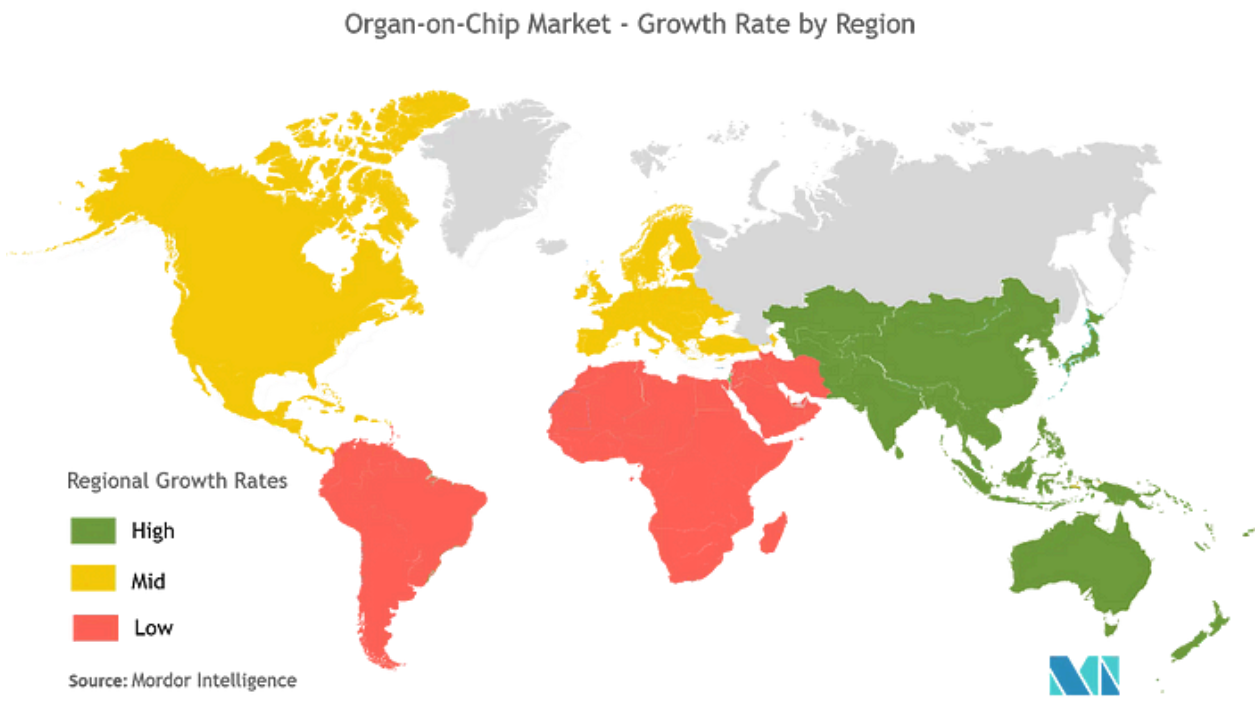
Source: BIOLINES LABORATORY/UNIVERSITY OF PENNSYLVANIA

FDA

This program falls under the core decisions of the FDA to strategize plans for regulatory science. FDA's main mission is to protect the consumers by applying the best possible science and technology to its regulatory activities. This involves a pre-market review of efficacy and safety and post-market product surveillance for the review of product quality. They concentrate on 9 areas that they recognize as essential to advance its mission:[21] And this is overseen by the Office of Regulatory Science and Innovation. The technology Organs-on-chips was a part of this mission. It aided two areas. 1)Modernize Toxicology to Enhance Product Safety and 2) Facilitate Development of Medical Countermeasures to Protect Against Threats to the U.S. and Global Health and Security. FDA, in addition to upholding responsibilities of protecting public health, also invests in research innovations that will in-turn help them in their regulatory processes.[22]

Apart from the research investments, collaborations, contracts, fundings, etc that are made by the FDA for this technology, it is also organizing programs to promulgate this platform. In the year 2018, FDA's toxicology division and Center for Food Safety and Applied Nutrition (CFSAN) laid a roadmap for implications and opportunities for Stakeholders in Predictive Toxicology through a presentation by Dr. Suzanne Fitzpatrick, Ph.D., DABT, ERT, Senior Advisor for Toxicology.[23] In this, the speaker covered pressing issues related to toxicology studies. It discussed the advances in systems biology, stem cells, engineered tissues, and mathematical modeling being the potential breakthrough for replacing, reducing, and refining animal studies.

The roadmap laid a 6-part framework for integrating these avant-garde predictive toxicology methods into safety and risk assessments of its products. This presentation detailed FDA's collaborations with NIH, EPA, and other federal agencies through programs like Toxicology Testing in the 21st Century termed as Tox21 and ICCVAM programs. It advertised the organs-on-chips technology and its pathway and to now being an established innovation. This opened the door to many start-up companies for manufacturing this technology vis-à-vis Elveflow, Mimetas, Fluigent, EmulateBio, AxoSim, Inc., BiomimX SRL, Hurel Corporation, and many more. From the market research, it is expected to have a CAGR of 12.3% by the year 2025.[24]



Source : [Mordor Intelligence]

This way FDA encouraged diverse stakeholders to work with the agency to share ideas, discuss new technologies, and highlight collaborations that are developing and testing new methods.

To sum up the regulatory talk for this particular technology, a lot of startups are now selling kits and distributing this technology for the research as discussed. So where does this leave with FDA approval? In the United States, a cooperative research and development agreement (**CRADA** or CRDA) is an agreement between a government agency and a private company or university to work together on research and development. Organs-on-chips was a result of this. Most of the companies that are now commercializing this product are through an agreement with CRADA. The licensing of their proprietary technology will be under specific licensing conditions, mainly confidentiality. Other terms of the license agreement will state that the results cannot be used for the treatments of humans. From this, we can understand how the FDA, CRADA encourages the companies to expand their research within the bounds of safety. [25]

Conclusion

To conclude on the topic, I want to provide some highlights and hitches. With a hike in product development and globalization, there is a need to advance regulatory science and keep up with the pace. The priority of this technology was in improvising modern toxicology for preclinical safety predictions, models of human adverse response, identifying and testing for biomarkers to track toxicities, computational tools, and in-silico modeling. The goal is to lead towards a novel toxicity testing that depends less on animal testing and more on in-vitro methods.

Advances in micro-physiological systems that can mimic functional units of cells, tissue, and organs are a pathway to achieve this vision. We learned about the types of organ chips and its mechanism that can reflect human physiology and anatomy. The organization's funding and involvement in the research were summarized. The journey of this chip from lab to industry was summarized. FDA coordinated with various federal and research institutions on how to best develop this blooming chip technology. The involvement of the regulatory division aided the research to help address the bottlenecks in knowledge needed to regulate this product.

FDA has high trust from the public to make sound decisions and put out high-quality products on to the market owing to their transparent review process and advanced tools to assess safety and risk. Due to this responsibility, the FDA is always on track to identify, develop, validate, and integrate new technologies into the regulatory process through collaborations with govt. researchers, industry, academia, and stakeholders.

Having said that, it is also true that not all technologies are pertinent to use for regulatory science especially when it has to be conformed to strict regulatory demands for producing results that can affect public health. Looking up to the Qualification and Validation process that is linked to the

regulations, any new tool must comply with this to make safety decisions that potentially can affect millions of consumers. It is also important that the application of a new tool has to be done without needing to review the supporting research data each time the tool is used. The key here is establishing confidence in the tool as “gold standard”. To infer, a considerable amount of work has to be done before any technology can become the new regulatory research tool.[26]

In the end, thank you all for taking the time in reading. I hope it was informative and interesting. Any inputs, thoughts, or comments are most welcome. I work closely with this technology and am awaiting to dive deep into its unexplored potential.

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