DATE: December 21, 2021
TO: Michael Severino, M.D., Vice Chairman and President
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SUBJECT: White Paper: Organ-Chips in Biologic Development

Executive Summary: the Organ-Chip Opportunity

Background: Abbvie and the Future of Organ-Chips

Abbvie is a huge player in the biologics market, having the best-selling drug globally, Humira. Founded in 2013, the publicly traded biopharmaceutical company originated from a split-off from Abbott Laboratories. Innovation through research and development has always been a priority for Abbvie. Abbvie's current therapeutic focus areas include: immunology, oncology, neuroscience, eye care, virology, and aesthetics.

Within the last 15 years, the combining of labs-on-chips with advances in cell biology has produced organ-chips as a technology poised to radically transform the pharmaceutical industry. Organ-chips, which model organs such as the brain, liver, kidney, lungs, and small and large intestine, present an opportunity to drastically improve preclinical testing during drug development. Abbvie has the potential to partner with Emulate Inc., a pioneering company in organ-chip development, to move the organ-chip technology forward from the lab to industrial use in the pharmaceutical industry.

Summary: Abbvie and the Future of Organ-Chips

Opportunity Analysis: Limitations to the Status Quo

Getting a drug to market is a significant problem in the pharmaceutical industry: it's expensive, time-consuming, and often ends in failure. A major cause of this problem is preclinical trials that don't accurately predict clinical outcomes in humans. The two major models for preclinical testing are classical cell cultures and animal models. Both have drawbacks: the classical cell cultures are two simplistic to realistically model the physiology of human organs, and animal models introduce species differences. Three-dimensional cell culture technologies such as spheroids and organoids are more promising, but still don't represent the necessary level of complexity required to simulate drug interactions with the human body.

Abbvie's patent for Humira is set to expire within a few years. While its hold on the market continues, it would be prudent to continue to focus efforts on expanding Abbvie's portfolio of biologics by increasing new biologic discovery.

Opportunity Fulfillment: An Overview of Organ-Chip Technology

Organ-chips present an opportunity in four major areas of study that aid drug discovery:

- Modeling mechanisms of disease
- Identifying biomarkers
- Screening drug candidates
- Toxicity testing

Adoption of the organ-chip technology is at an early stage, but the technology holds promise for accelerating drug discovery and development, replacing animal testing, and playing a part in the future of medicine: personalized medicine. Organ-chips are set to revolutionize the pharmaceutical industry through their improvements in the drug discovery process.

Partnering with Emulate to improve the organ-chip technology for industrial use would provide a double opportunity for Abbvie: First, it would speed up the opportunity to use this improved technology for Abbvie's drug discovery, hopefully decreasing research and development resources needed, and second, it would improve Abbvie's reputation as an innovator, furthering human knowledge of hard-to-treat diseases.

Biotechnology Industry Overview

Industry Profile

Industry Description

The global biotechnology industry uses living organisms and molecular biology to develop products used in agricultural, food, industrial, and medicine production [1]. It comprises companies involved in diverse activities, from vaccines, biopharmaceuticals, and diagnostic tests to the development of biofuels and pest-resistant crops.

Industry Performance: Current and Historical

In general, the biotechnology industry is volatile, as many biotechnology products and companies have a high probability of failure [1]. The global biotechnology industry was valued at $627.6 billion (USD) in 2020. The industry weathered the fallout of the pandemic during 2020, as it was part of the generation of COVID-19 vaccines and treatments. Falling global investor confidence from 2016 until now has limited revenue growth in the industry. Demand for biofuels has been depleted by the lack of incentive to develop cheaper alternatives to fossil fuels because of lower fuel price [1]. *Figure 1* provides the biotechnology industry yearly value from 2013 to 2020.

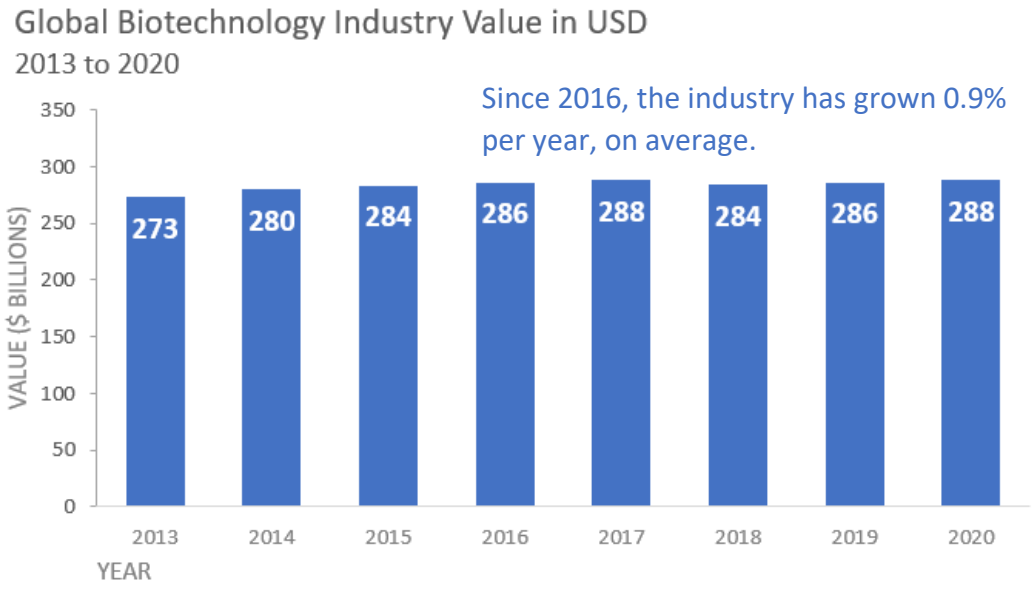

FIGURE 1. GLOBAL BIOTECHNOLOGY INDUSTRY VALUE 2013 TO 2020. ADAPTED FROM [1].

The market size of the industry is expected to increase 3.6% in 2021 [2]. For 2021, in rankings of Global Business Activities industries, the global biotechnology industry is the 44th largest, and is ranked 6th by market size [3]. Since half of industry revenue comes from biotechnology products for human health, it will benefit from an increase in 2021 of the number of adults aged 65 and older, who spend more on healthcare, including biotechnology health products [1].

The biotechnology industry is knowledge-intensive, making it dependent on competition from other areas of research and the priorities of governments. In 2021, global investor confidence was expected to increase, making it more likely that new biotechnology projects and start-ups received funding [1].

Industry Outlook and Forecast

The global biotechnology industry is expected to have an increased rate of growth over the next five years as countries in the Asia-Pacific region invest large amounts of capital to increase their presence in the industry. As global research and development and total health spending are predicted to grow, industry revenue is forecast to increase at an annual rate of 3.1% to $347.3 billion (USD) by 2026 [1], with a CAGR of 8.57% from 2021 to 2026 [2]. See *Figure 2*.

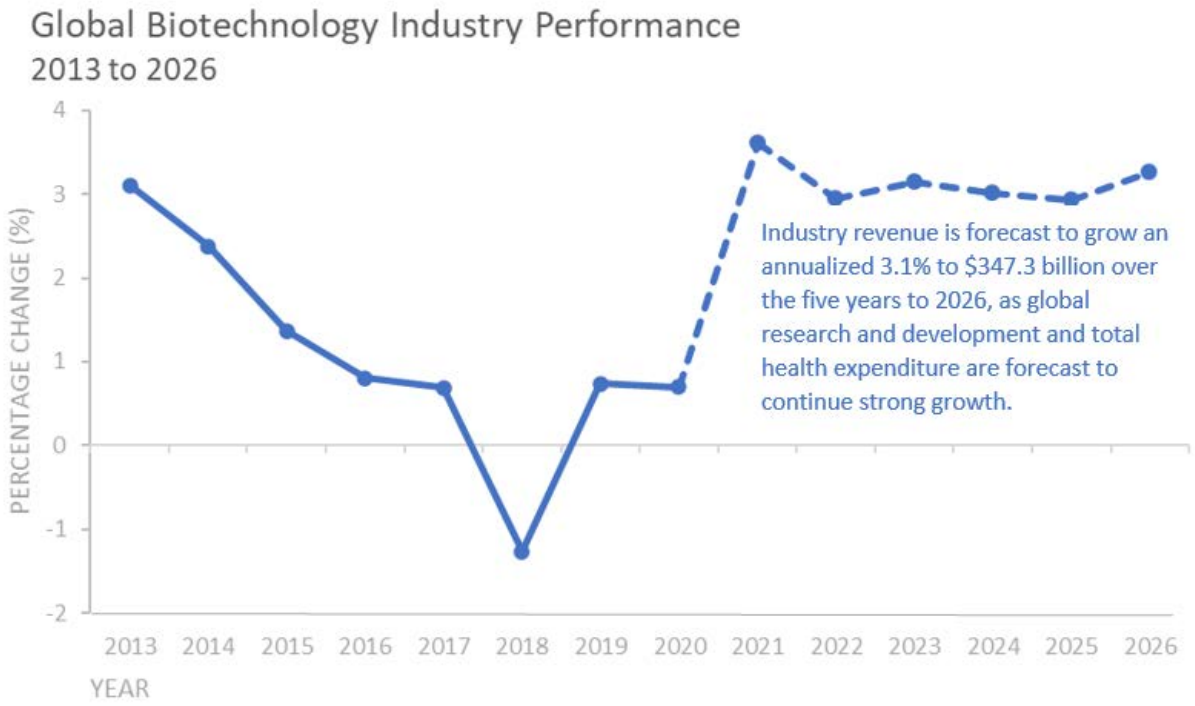

FIGURE 2. GLOBAL BIOTECHNOLOGY INDUSTRY PERFORMANCE, 2013 TO 2026. ADAPTED FROM [1].

Industry Segmentation

The industry is segmented by products and services into five segments: human health technologies, industrial technologies, animal health technologies, agricultural and environment technologies, and other. See *Figure 3* for the percentage share of each segment to the overall industry revenue for 2021.

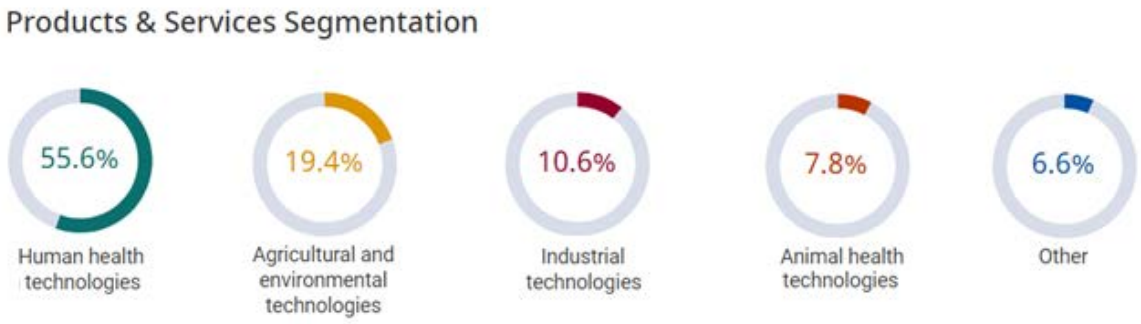

FIGURE 3. BIOTECHNOLOGY INDUSTRY SEGMENTATION, PERCENTAGE SHARE BY VALUE, 2021 [1].

Human Health Technologies

The human health technology segment of the biotechnology industry made up the majority of industry revenue in 2021, at 55.6% [1]. The products are mainly therapeutics, such as biologics (or biopharmaceuticals); medical diagnostics, such as tests for specific gene or protein markers; and preventatives, such as vaccines developed from recombinant DNA methods [1], [4]. The healthcare products produced mainly target diseases that have no small-molecule (chemical) treatment available such as autoimmune diseases and cancer.

The human health technology segment's share of revenue has grown over the past five years. The industry seeks to expand into elective treatments, such as for obesity; sales are predicted to increase because of the larger elective treatment market size[1]. As well, the future of medicine, pharmacogenomics (or personalized medicine) is included in this sector, contributing to its expected growth [4].

Agricultural and Environmental Technologies

Agricultural biotechnology products enhance production, complementing or replacing chemical equivalents. Crops such as soybean, maize, and cotton are engineered to have desirable characteristics: to be resistant to pests, or nutrient dense, or use nitrogen more efficiently, or tolerate stress, drought, or frost. Due to ongoing investments into crop production and agriculture research and development, this segment has grown over the past five years to an expected 19.4% of industry revenue in 2021 [1].

Industrial Technologies

Industrial biotechnology covers many sectors including textile, food, and energy. It's expected to comprise 10.6% of the biotechnology industry revenue in 2021 [1]. There is a focus on using technology to create new processes using fewer natural resources [4]. There has been an increase in demand for this sector as nations seek to benefit their economies by reducing crude petroleum imports and replacing them with liquid biofuels, stimulating rural economies through increased agricultural crop consumption [1].

Animal Health Technologies

Over the past five years, animal health technologies have fallen in percentage of revenue to be an estimated 7.8% in 2021. The applications in this segment are similar to those in human health, but the market is much smaller for animals. Concern over applications of biotechnology in farm animal breeding has contributed to the decline in revenue over the past five years. Microbes are an increasing interest in this segment, as they hold promise in diagnostic tests and antibiotics, and the synthesis and sequencing of proteins and peptides [1].

Other

The other products and services in biotechnology account for 6.6% of revenue in 2021. They include bioinformatics and other application fields. Bioinformatics includes the building of databases of genomes and protein sequences, and the modeling of complex biological processes [1].

Target Market Analysis: Biologics

Market Description

The biologics market consists of sales by entities that produce biologics or biosimilars to treat chronic diseases, including cancer. These products include recombinant therapeutic proteins, gene therapy tissues, somatic cells, vaccines, and allergenics [5]. While small-molecule (chemical-based) drugs are still around 90 percent of all drugs available on the global market, biologics are nearly one third of global drug sales [6].

Biologics have revolutionized healthcare, offering important advantages over small-molecule pharmaceuticals:

- They are able to treat diseases that had were previously considered untreatable.
- They offer target specificity and better therapeutic efficacy, resulting in better safety profiles [7].

The biologics market is segmented by type into:

1. monoclonal antibodies (mAbs)
2. therapeutic proteins
3. vaccines

Market Performance: Current and Historical

Growth in the market has historically stemmed from the aging population, government initiatives, ability to maintain high prices, and the growing need for immunology [5]. In 2018, biologics were eight of the top ten bestselling drugs worldwide. In 2020, the global market for biologics was $285.5 billion (USD) [8]. See *Figure 4* for the leading biotech drugs by revenue worldwide for 2020. From 2015 to 2019 the market's compound annual growth rate (CAGR) was 12.5% [5].

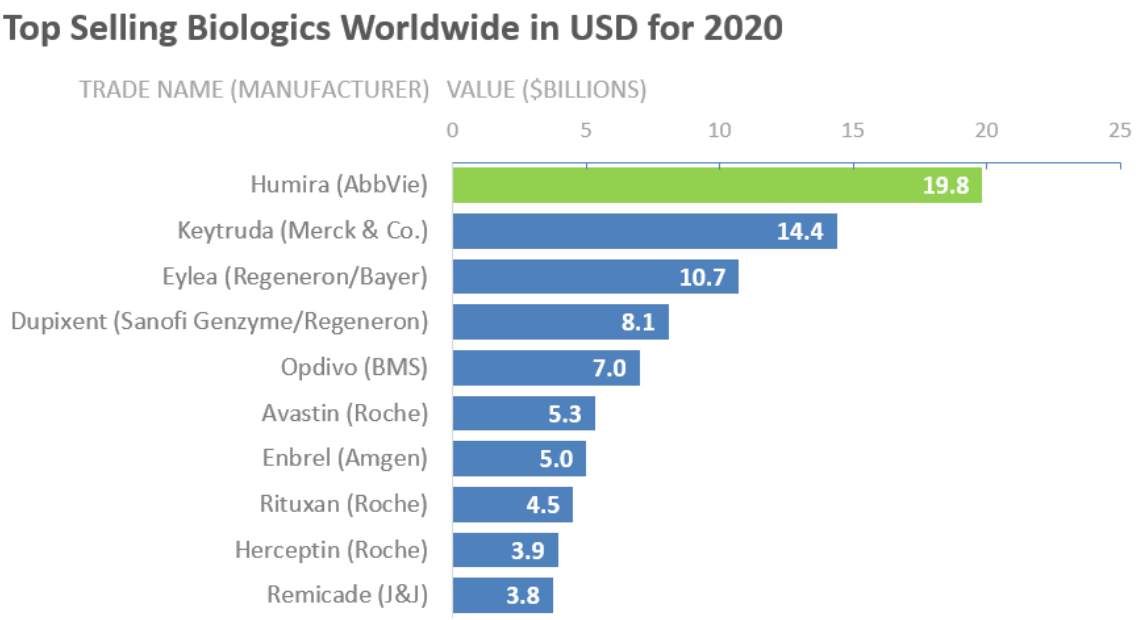

FIGURE 4. LEADING BIOLOGICS BY REVENUE WORLDWIDE FOR 2020. ADAPTED FROM [9].

Market Outlook and Forecast

The original generation of biologics are losing their patent protection, and will face more competition as biosimilars (pharmaceuticals that have similar properties to an already approved drug) enter the market. To reduce healthcare costs, governments around the world are increasing the demand for biosimilars [10].

The global biologics market is expected to grow from $253.4 billion (USD) in 2020 to $268.5 billion (USD) in 2021, with a CAGR of 6%. By 2025, the market is expected to reach $420.6 billion (USD), with a CAGR of 12%. The largest market for biologics by geography is North America; the fastest growing market is Asia Pacific [11].

Market Segmentation

The biologics market is segmented into monoclonal antibodies (mAbs), vaccines, recombinant proteins, hormones, growth factors, and others. Of the segments, mAbs generate the largest share of revenue due to their application in the treatment of cancer, and are the focus of pharmaceutical companies. The monoclonal antibodies market was the largest segment (by type) in 2019, accounting for 42.6% of the market.

The market is predicted to have a CAGR of over 7% from 2020 to 2024, growing by $54.6 billion (USD); biosimilar monoclonal antibodies are a main reason for this growth [12].

Market Characteristics

The biologics market is highly competitive and is fairly fragmented (see *Figure 5*); although it's dominated by a few large companies, mid-size to smaller companies enter the market through technological advancements and product innovations [13], [14]. There will be increasing competition for the major players due to patents on some highly profitable biologics expiring.

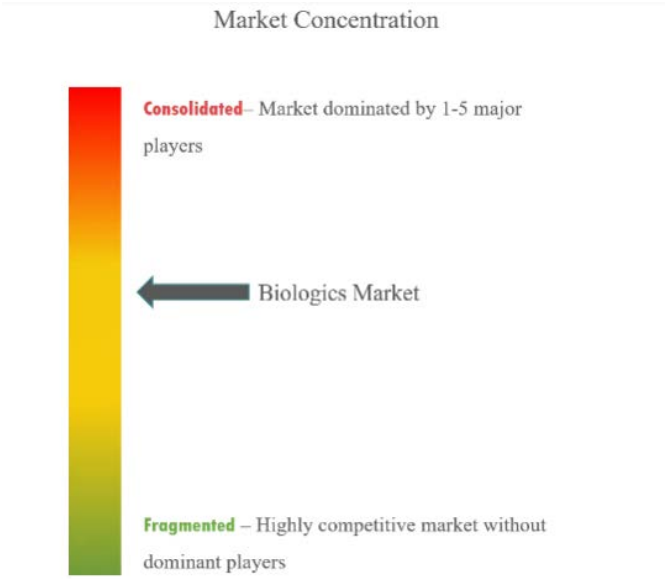

FIGURE 5. GLOBAL BIOLOGIC MARKET CONCENTRATION [11].

Market Features

The following features characterize the biologics market:

- **Difficult and costly to manufacture:** Biologics are highly complex molecules that are difficult to manufacture, requiring a highly educated and specialized work force. The high cost of manufacturing makes biologic drugs extremely expensive, which will hamper their adoption in emerging markets where the consumer is less likely to have reimbursement resources available to them [15].

- **Expected biosimilar shake up:** Biologics are expensive and complicated to develop. Patents give an opportunity to get return on investment, but several biologic patents for the original biologics (such as Abbvie's Humira) have recently expired, or are set to expire soon. Biosimilars are similar to a biologic, but are not identical, and cannot be considered generic versions; because of the natural variation of biosimilars, there is a longer and more costly approval process than for generics.

Biosimilars are typically priced at a discount of 10% to 30% of the originator's version; however, prices continue to fall as additional biosimilars enter the market and the originators respond with price cutting. There is growth in the share of biosimilars in the biologic market, but it's smaller than expected, as the growth of biologics in markets with no competition from biosimilars yet has made up for the loss of market [16].

- **A fairly fragmented market:** Small enterprises are drivers of drug discovery and manufacturing of biologics. These companies are often acquired by large pharmaceutical companies as an attractive alternative way of gaining know-how and promising new therapies without the investment into in-house research and development [6].

Market Trends

The following trends exist in the biologic market:

- **Emphasis on research and development:** Market leaders are continuously searching for new and effective biologics through research and development. These activities have resulted in increasing success rates in clinical trials [5] .

- **Demand for treatment of complex diseases and rising acceptance of biologics:** Diseases that have previously had limited treatment options, such as rheumatoid arthritis, psoriasis, and inflammatory bowel disease (Crohn's and ulcerative colitis) are now widely being treated by biologics. Biologics offer alternatives to surgical treatments and allow patients to avoid the side-effects associated with small-molecule pharmaceuticals [5].

- **Demand for Oral Delivery:** Biologics are 200 to 1,000 times the size of small-molecule (chemical) pharmaceuticals. They are mostly delivered through parenteral routes. The demand for development of oral biologics, rather than injection or intravenous delivery will drive growth [17].

Market Catalysts

The following agents are driving the biologic market:

- **Technological advances and capital investment:** Technology that enhances the research and development of biologics is a driver of market growth. For example, physiology simulation modeling: Eli Lilly and Pfizer are conducting simulation models in early drug discovery using Amazon's Elastic Compute Cloud (EC2) platform; this simulation model operates within hours, rather than the weeks it would take usually to perform simulations [10].

- **Rise in the burden of chronic diseases:** According to the World Health Organization, chronic diseases kill 41 million people each year. Cardiovascular diseases, cancers, respiratory diseases, and diabetes account for 80% of all chronic disease deaths. The rise in age of the population and unhealthy lifestyles due to tobacco use, lack of physical activity, alcohol consumption, and unhealthy diets all contribute to the increased susceptibility of the population to chronic disease, which increases demand for biologics [11].

- **Easing of regulations:** At 53% of the market in 2020, North America was the largest region in the global biologics market. The U.S. Food and Drug Administration (FDA) revised its regulations, allowing manufacturers to use new manufacturing and testing capabilities, removed minimal potency limits, and updated regulations regarding storage of biologics [10].

- **Impact of COVID-19:** Extensive research and development on biologics for the pandemic is driving growth in the market for the near future. The largest segment of the market, mAbs, has experienced positive impact from COVID-19, as several mAbs have potential to treat the disease. Clinical trials are being conducted. The FDA issued emergency use authorization (EAU) for the use of a combination of mAbs for treatment of mild to moderate infection. Roche received EUA for the same combination by India's Central Drugs Standards Control Organisation. Some firms have entered into collaborative agreements, in order to minimize the impact of disruptions to development and distribution of biologics during the pandemic. These new therapies to fight the virus will drive mAbs market demand [18].

Competitive Landscape Structure

Key Players

Abbvie Inc., Amgen Inc., Eli Lilly and Company, F.Hoffman-La Roche AG, and GlaxoSmithKline PLC are major players in the biologics market.

Table 1: Comparison of key players in the biologics market [19]–[32]

Company	Area of Expertise	Strengths	Weaknesses	Annual Revenue For 2020 (Billions USD)
F.Hoffman-La Roche AG	• Oncology, neurosciences, rare diseases, immunology, infectious diseases, hematology, hemophilia, and respiratory diseases • Entering new markets	• High investment in research and development • Reliable suppliers Good returns on capital expenditure	• Gaps in product range • Weak product demand forecasting • High attrition rate	62.3
Abbvie Inc.	• Immunology, hematologic oncology, neuroscience, allergan aesthetics • Research and development	• High margins • Track record of innovation and strong pipeline • Strong technological capabilities • Market leadership position	• High reliance on revenues from Humira • Public relations issues • Threats from biosimilars	45.8
Amgen, Inc.	• Oncology/ hematology, cardiovascular disease, inflammation, bone health, nephrology and neuroscience • Entering new markets	• Strong distribution network • Successful integration of complimentary firms • Highly skilled workforce	• Lower investment in research and development than competitors • Limited success outside core business	25.4

Company	Area of Expertise	Strengths	Weaknesses	Annual Revenue For 2020 (Billions USD)
Eli Lilly and Company	• Bone muscle joint, cancer, cardiovascular, diabetes, endocrine, immunology, neurodegeneration, neuroscience, and pain	• Strong brand portfolio • Combined strengths in pharmaceuticals and diagnostics	• Needs innovation through more investment in new technologies	
GlaxoSmithKline PLC	• Vaccines, respiratory diseases, HIV, infections diseases • Over-the-counter, oral health segments • Marketing	• Research and development capabilities (including external partnerships and collaborations) • Global sales and marketing	• Brand image affected by legal issues • Patent expiration	15.1

The Abbvie Sustainable Competitive Advantage

AbbVie is a huge player in the biologics market. The company has had multiple years of excellent growth, largely due to its flagship biologic, Humira, the top-selling drug globally (see *Figure 4*). However, two events could impact Abbvie's continuing success:

- Humira will be losing patent protection in the United States in 2023.
- A report released in May of 2021 by the House Oversight and Reform Committee found that Abbvie engaged in anticompetitive pricing practices [33].

In light of these events, a strategic partnership with Emulate to develop organ-chips for industrial use in the pharmaceutical industry could provide the following long-term advantages for Abbvie:

- **Better predictive value in modeling clinical outcomes:** Production of new biologics is complex and costly; however, once approved they are highly profitable assets [33]. Approximately nine years of research and development and a lot of capital investment are required to bring a product to market [34]. Preclinical ADME-Tox (Absorption, Distribution, Metabolism, Excretion, and Toxicity) studies are crucial to predicting human response. Approximately 30% of drugs fail human clinical trials due to adverse reactions, and 60% due to lack of efficacy [35]. Once organ-chips are ready for industrial

use they will provide better predictive value in modeling clinical outcomes, reducing drug development costs.

- **Improved public relations:** Organ-chips could revolutionize drug development, but researchers can also use them to further knowledge of organ function and pathogenesis. By working with Emulate to develop organ-chips to the point they can be used beyond academic research, Abbvie will be following through on its commitment to its principles: “we invest and innovate relentlessly to tackle unmet needs, creating new medicines and healthcare approaches for a healthier world” [37].

- **Better modeling of oral delivery:** Unlike small-molecule pharmaceuticals, biologics are large, complex molecules that degrade rapidly in the gastrointestinal (GI) tract. There is an increasing demand for oral delivery from patients because of its lower cost and convenience; most biologics are currently delivered by parenteral routes. The GI tract organ-chip models can determine the bioavailability of an oral drug in blood circulation [38].

- **Ethical advantage - reduction of animal usage in testing:** As well as not being reliably predictive of human response, use of animal models in preclinical drug screening is expensive, time-consuming, and raises ethical issues. The ban on animal testing for consumer products in Europe is likely to spread worldwide, requiring a shift away from animal testing; organ-chips provide an ethical alternative.

Opportunity Analysis: Organ-Chips in Biologics Discovery

Limitations to the Status Quo

The limitations of the status quo for preclinical testing point to the need to develop organ-chips for drug discovery.

Overview of Preclinical Testing

Bringing a drug to market requires years of research and an increasing level of capital investment, and often ends in failure. While the average time for a drug to go through clinical trials has decreased, the rate of success has decreased by almost half, to 12 percent [39]. A major reason for this is preclinical trials that don't adequately model how the human body will react during clinical trials.

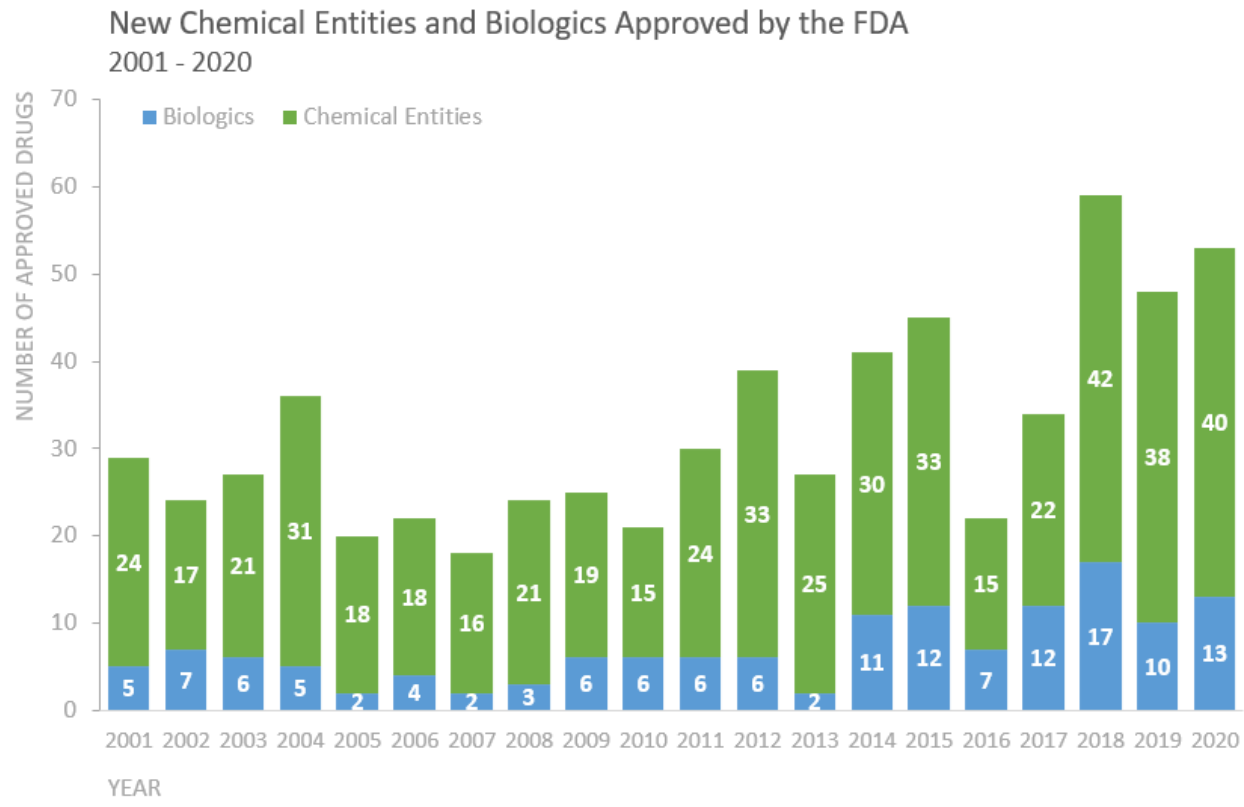

FIGURE 6. DRUGS APPROVED BY THE FDA IN THE LAST TWO DECADES. ADAPTED FROM **[40]**.

Limitations of Current Preclinical Testing Methods

Two major models have historically dominated preclinical testing: classical cell cultures and animal model systems. These two systems have driven biomedical research from the late twentieth century and continue to be useful today. They have helped with the understanding of cellular signalling pathways and the design of potential drugs for both infectious diseases and cancer [41]. However, extrapolating results from these models to humans is a major hurdle in drug discovery. Three-dimensional (3D) cell culture technologies are emerging as new tools for this purpose: they include spheroids, organoids, scaffolds, hydrogels, organs-chips, and 3D bioprinting.

Classical Cell Cultures

Two-dimensional (2D) monolayer cultured cells on planar substrates are still an effective way of predicting *in vivo* drug responses. However, classical cell cultures fail to model the interaction of cells with their original environment: the effects of tissue-specific architecture, mechanical forces, biochemical cues, and cell-to-cell and cell-extracellular matrix interactions are missing [42].

Animal Models

While animal models provide a *in vivo* model for human disease by providing proof-of-concept for safety and efficacy, there are still species differences that contribute to the poor translation rate to successful clinical trials. There are also ethical issues with using animal studies for preclinical research. For biologics such as monoclonal antibodies, the only suitable model is non-human primates: use of primates is especially difficult due to lack of supply, expense, and the practice is controversial [43].

Three-Dimensional (3D) Cell Culture Technologies

Recent advances in microfabrication techniques, cell biology, and tissue engineering have allowed for the development of *in vitro* models that more closely emulate the environmental features of human tissues and organs [42]. *Figure 7* shows how these technologies are being used in drug discovery.

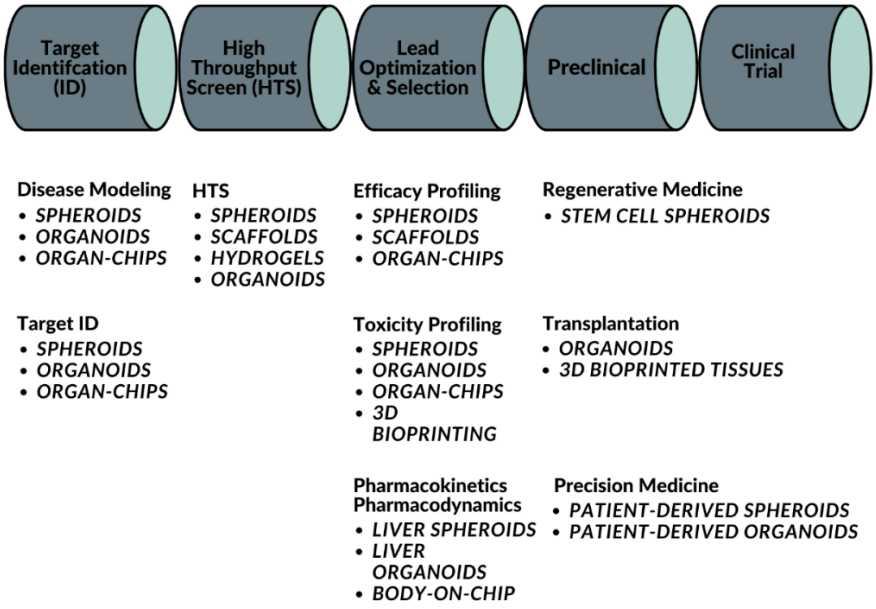

FIGURE 7. HOW 3D CULTURE TECHNIQUES IN DIFFERENT STAGES OF DRUG DISCOVERY. ADAPTED FROM [42].

Spheroids

Spheroids are 3D cell cultures that arrange themselves during proliferation into sphere-like shapes. Multicellular spheroid cultures compensate for many issues with monolayer cultures. Due to their ability to develop gradients of oxygen, nutrients, metabolites and soluble signals, they can create heterogenous cell populations. They also replicate cell-cell and cell-extracellular matrix interactions [42].

Some challenges with spheroids include:

- Maintaining size uniformity, which is crucial for getting reproducible results. The use of 3D bioprinting automation helps with this [44].
- The precise control of specific ratios of different cell types.
- The lack of reliable, simple, standardized, and high-throughput compatible assays for drug screening using spheroids [42].

Organoids

Organoids are dish-based, 3D developing tissues that mimic some of the structure and function of human organs. They are groupings of organ-specific cell types that develop from stem cells and organize themselves similar to *in vivo*. Functional organoids have been developed to model several organs, including thyroid, pancreas, liver, intestine, lung, and retina [42].

Some challenges with organoids include:

- They lack of vasculature, which models nutrient and waste transport.
- They lack of some important cell types found *in vivo*.
- Some organoids only emulate the early stages of organ development.
- Achieving reproducibility to the level needed for drug screening.

Significance of Limitations on Stakeholders

The limitations of current preclinical testing methods directly impact the following stakeholders: patients, researchers, and the biologics industry.

- **Impact on patients:** Ineffective preclinical testing slows down the drug discovery process, delaying the introduction of new safe, efficacious biologics to the market. Biologics, in particular, target previously untreatable diseases such as Crohn's disease, ulcerative colitis, rheumatoid arthritis, and other autoimmune diseases. Delays in potential breakthroughs for currently untreatable conditions prolongs the suffering of the affected patients.

- **Impact on researchers and clinical trail participants:** The limitations of current preclinical testing mean dangerous or ineffective treatments are not screened out early in drug discovery and promising candidates may be missed. This means that researchers' time is wasted and that clinical trial participants are at higher risk for bad outcomes.

- **Impact on the biotechnology industry:** Research and development is a huge cost to the biologics industry; spending has grown by more than three times the rate of the drug industry during the last twenty years [45]. Preclinical testing that doesn't accurately predict clinical trial results contributes to wasted resources during drug development.

Significance for Abbvie

The U.S. Food and Drug Administration (FDA) regulates small-molecule and biologic drugs differently. For example, Lipitor (atorvastatin), a cholesterol-lowering small-molecule drug is made up of 76 atoms is very cheap to manufacture. Abbvie's monoclonal antibodies biologic, Humira (adalimumab), is a large-molecule drug made up of 20,067 atoms. Biologics are complex proteins manufactured in living cells: a much more expensive process requiring highly skilled workers. Because of this the FDA regulates the two categories differently [46].

Small-molecule drugs are governed by the Food, Drug, and Cosmetic Act, while large-molecule drugs are governed by the Public Health Service Act. While both acts treat the two categories of

drugs similarly in terms of requirements for clinical trials and regulation of manufacturing, the FDA regulation differs for the two categories after patents expire [46]. Currently, Abbvie benefits from these differences, as it makes it very hard for manufacturers of biosimilars to enter the market. However, if the US government begins to reform prescription drug prices biologics will be a major target, as since 2014, biologic drugs make up 93% of all growth in net drug spending in the U.S.

The continuing dominance of Humira on the drug market has caused continual steep price raises. Abbvie has won many more patents since the initial expiration in 2016 [47] . Abbvie's focus on maintaining this monopoly raises ethical and public relations issues: high costs of biologic drugs mean less patient access. Abbvie needs to increase efforts to expand its portfolio through new drug development. Progress in accelerating research and development and decreasing the probability of failure at the clinical trial stage is currently hampered by inadequate preclinical testing methods.

Currently, the main use for organ-chip technology is in academia in research of physiology. There are technological advances needed to move this technology into industry. The Technology Readiness Level (TRL) for organ-chip technology is TRL4, which corresponds with validation in the laboratory environments. TRL9 would be needed for it to be adopted for industry [47].

There are three major areas of drug development which are lacking in current preclinical testing methods, to which organ-chips can contribute:

1. Mechanistic investigation: organ-chips will allow for rapid assessment of drug mechanisms for pharmacology of toxicity [47].
2. Preclinical safety screening: providing *in vitro* prediction of toxicity before clinical trials so that high risk candidates can be ruled out [47].
3. Drug absorption, distribution, metabolism, and excretion (ADME): ADME assays give insight into drug metabolism and interactions with other drugs [47].

Opportunity Fulfillment: Organ-Chips in Biologics Discovery

Organ-Chip Technology Architecture

Organ-Chip Overview

An organ-chip is a multi-channel, three-dimensional cell culture used in biomedical engineering research as an *in vitro* emulation of an organ. About the size of an AA battery, organ-chips are relatively inexpensive and can be mass produced, but allow for more physiological relevance than classic *in vitro* models. Emulate currently produces six organ-chips: Brain-Chip, Colon Intestine-Chip, Duodenum Intestine-Chip, Kidney-Chip, Liver-Chip, and Lung-Chip. *Figure 8* shows a diagram of Emulate's Liver-Chip.

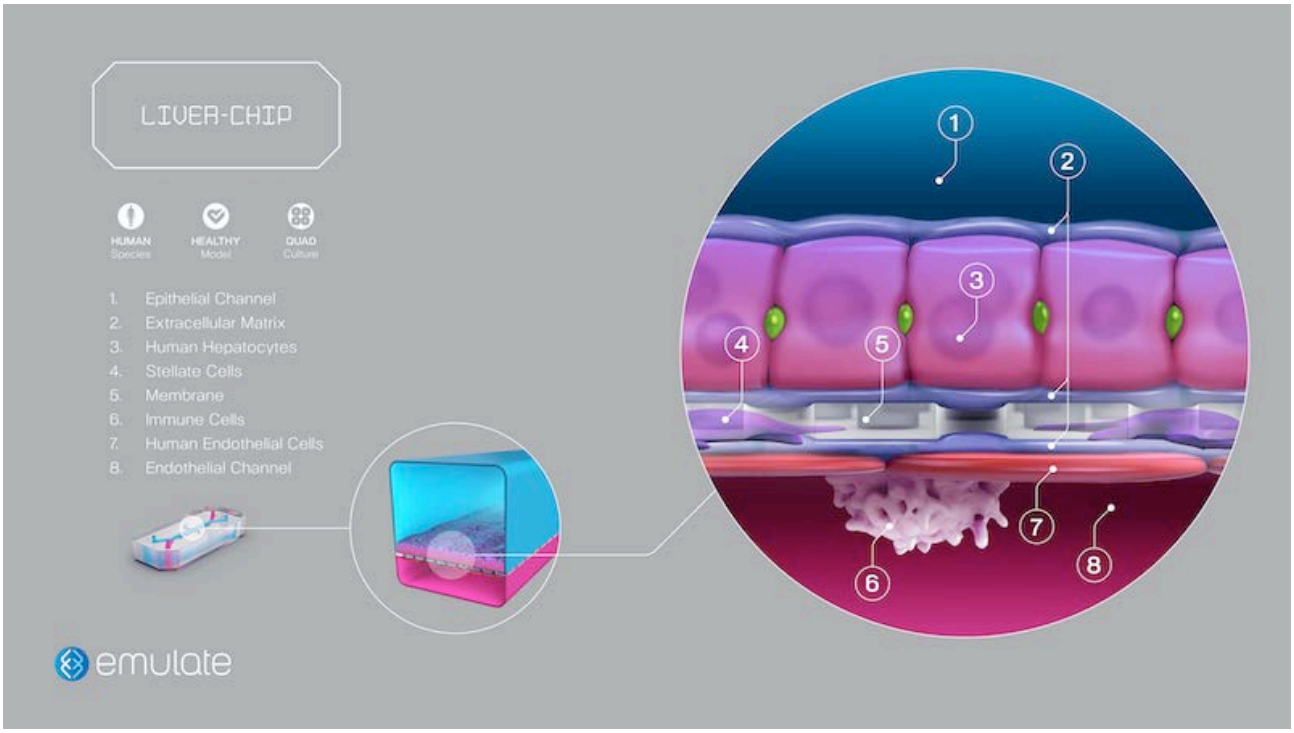

FIGURE 8. DIAGRAM OF A LIVER-CHIP FROM EMULATE BIO [43].

Description of Organ-Chips

Emulate's organ-chips are made of clear flexible polymer with two channels. The flexible polymer enables cyclic stretch which allows for modeling of mechanical forces such as

breathing and intestinal peristalsis. Human cells are cultured and nutrient media flow through the two channels, allowing the model to emulate cell-cell interactions.

FIGURE 9. EMULATE'S ORGAN-CHIPS [51].

Organ-Chip Solution Provided by Emulate

Emulate provides a solution incorporating instruments, consumables, and software. Each organ-chip is housed in a pod, which enables the interface between the organ-chips and Zoë-CM2™ Culture Module (a system to automate the conditions such as media flow rates and stretch parameters for culture), and contains the media and effluent [51].

Brain-Chip

Emulate's Brain-Chip is a model of the cortical brain tissue, consisting of five cell types, including neuronal cells, in an adjustable microenvironment. It is designed to help researchers look into the mechanisms of neuroinflammation and investigate blood-brain barrier penetration during drug discovery [50].

Colon Intestine-Chip

The Colon Intestine-Chip combines biopsy-derived organoids and colonic endothelial cells with mechanical forces to emulate the physiology of the human colon. The model was designed to research biochemical, genetic, and cellular responses during drug safety, disease modeling, and physiology studies. Due to the dynamic conditions created by the mechanical forces that emulate peristalsis of the colon, the cells differentiate and microvilli are formed, better modeling the intestinal barrier. Proinflammatory cytokines can be introduced to the chip to

recreate the mechanisms of colon inflammation and barrier disruption seen in Inflammatory Bowel Disease. Anti-inflammatory drug candidates can be evaluated using the model [53].

Duodenum Intestine-Chip

Emulate's Duodenum Intestine-Chip combines human duodenal organoids and small intestine microvascular endothelial cells with mechanical forces to simulate intestinal peristalsis. Gene expression of metabolism, digestion, nutrient transport, and detoxification is superior to organoids alone. The main cell types of intestinal epithelial cells including absorptive enterocytes, enteroendocrine cells, goblet cells, and Paneth Cells are present in appropriate ratios. The intestinal barrier is simulated with tight junctions and realistic permeability. The cellular architecture of the small intestine is replicated, including villi-like structures and a continuous brush border [51].

Kidney-Chip

Designed to help predict drug-induced kidney toxicity and drug interactions, Emulate's Kidney-Chip models the proximal tubule-peritubular capillary interface. The chip allows for multiple measurements to be taken to investigate biomarker discovery and nutrient metabolism in a long-term culture (up to 14 days) [52].

Liver-Chip

A major hurdle in drug discovery is the limited predictivity of liver toxicity for *in vitro* models. Drug-induced liver injury (DILI) remains poorly understood due to species differences. Emulate's Liver-Chip co-cultures four human cell types: primary hepatocytes, stellate cells, Kupffer cells, and liver sinusoidal endothelial cells. Livery morphology is replicated through the formation of branched bile canalicular networks with MRP2 efflux transporters. The Liver-Chip models *in vivo* albumin and urea secretion [55].

Lung-Chip

Emulate is developing two models—the Alveolus Lung-Chip and the Airway Lung-Chip—to model different lung tissue relevant to investigating pathophysiology and drug development. The Lung-Chips have co-cultures of primary human lung epithelial and endothelial cells on either side of a porous membrane, in a microenvironment that simulates cell-cell interaction,

flow, and stretch. The microforces provide relevant cell differentiation, allowing for cilia behavior and tight epithelial barriers [53].

Use of Organ-Chips

The FDA and Emulate, Inc. have entered into Cooperative Research and Development (CRADA) agreements to allow multiple studies in priority research areas in 2017 and 2020. The CRADA agreement involves the following studies:

- Using the Lung-Chip infected with multiple strains of SARS-CoV-2 to study the immune response and vaccine safety [48].
- Using the Brain-Chip to model Alzheimer's disease using cells from Alzheimer's patients to study potential toxicity and therapeutic effects of treatments [48].
- Using the Intestine-Chip to study the effect of drug residues from animal-derived foods on the human microbiome [48].
- Using the Liver-Chip to investigate patient susceptibility to drug-induced liver toxicity [48].

Organ-chips have been mostly used in academic research. To become useful in the pharmaceutical industry there needs to be a balance of continued increasingly biological accuracy of the complexity of human organs with optimization of quality control, reproducibility, standardization, capacity and ease of use [49].

The demand for technology that provides more predictive preclinical models will continue to grow. The ban on animal testing for consumer products in Europe is likely to spread worldwide, requiring a shift away from animal testing. Funding agencies have started an initiative to further the progress towards industrial use. The National Institute of Health (NIH) and the FDA, and members of the pharmaceutical industry have already invested in furthering the progress towards [49].

Organ-chips present an opportunity in four major areas of study that aid drug discovery:

- Modeling mechanisms of disease
- Identifying biomarkers
- Screening drug candidates
- Toxicity testing

Adoption of the organ-chip technology is at an early stage, but the technology holds promise for accelerating drug discovery and development, replacing animal testing, and playing a part in the future of medicine: personalized medicine [43]. It is set to revolutionize preclinical testing in the pharmaceutical industry [47].

Features and Functionality

Table 2 lists the features and functionality of the Organ-Chips Technology provided by Emulate.

Table 2: Summary of main Emulate Organ-Chip features and functionality [51].

Feature	Functionality
Co-cultures of human primary cells	✓ Living human cells enable better modeling of human organs than animal cells or immortalized cell lines. ✓ Co-culture of two or more cell types enables modeling of cell-cell interaction. ✓ In the future, there is the possibility of using patient-specific cells for personalized medicine.
Organ-specific microenvironment and mechanical cues	✓ Physical or chemical signals simulate the physiological microenvironment of different organs. ✓ Mechanical cues can simulate physiological and pathological activity. ✓ Mechanical stimulation increases cell differentiation, allowing for better simulation of adult tissue.
Transparency and flexibility	✓ Researchers can see the organ model functioning and its behavior and response at the cellular and molecular level. ✓ The flexible polymer used as the basis for the organ-chips allows cyclic stretch to emulate intestinal peristalsis and breathing.
Microfluidic channels with molecular scaffold	✓ The microfluidic channels reproduce blood or air flow, like in the human body. ✓ The scaffold allows the microfluidic channels to support multiple living cell types.
Human tumor microenvironment	✓ Models the infiltration of immune cells into the tumour microenvironment. ✓ Media flow and tissue-relevant stretch model the mechanical forces cancer cells experience. ✓ Tuning of the microenvironment allows for modeling of early stages of metastasis.
Optional integration of sensors	✓ Sensors can be used for high-throughput analyses.

Benefits of Organ-Chips in Biologics Discovery

Benefits for Patients

Table 3 contrasts the patients' benefits of enhanced preclinical testing provided by organ-chips over existing preclinical testing.

Table 3: Summary of patients' benefits of organ-chip solution over existing preclinical testing.

Limitation of Existing Preclinical Testing	Organ-Chip Solution	Benefits Provided
Doesn't adequately predict clinical testing results	Provides better modeling of *in vivo* organ function	✓ Allows for more rapid introduction of new efficacious biologics to the market ✓ Increased safety when the drug makes it to market ✓ Reducing costs of research and development could be a cost-saving passed on to the patients
Reduces drug candidates that can be considered	Increases drug candidates that can be considered	✓ Possibility for new treatments for currently untreatable medical conditions
Doesn't allow for furthering knowledge of organ functionality and pathogenesis	Allows for furthering knowledge of organ functionality and pathogenesis	✓ Organ models can provide insight into physiology and pathogenesis of the organs, which can further knowledge of causes and prevention of disease

Benefits for Abbvie and Other Stakeholders

Table 4 contrasts benefits of enhanced preclinical testing provided by organ-chips over existing preclinical testing for researchers, the biologics industry, and Abbvie.

Table 4: Summary of Abbvie's and other stakeholders' benefits of organ-chip solution over existing preclinical testing.

Limitation of Existing Preclinical Testing	Organ-Chip Solution	Benefits Provided
Classic cell cultures have limited cell types	Provides co-cultures of relevant cell types for the organ being simulated	✓ Allows for modeling of cell-cell interaction ✓ Provides a model that's closer to *in vivo*
Classic cell cultures lack 3D architecture	Provides 3D architecture	✓ Allows for modeling of tissue-specific architecture of the organ ✓ Allows for mechanical and biochemical cues, and cell-cell and cell to cell-extracellular matrix interactions
Animal testing introduces species differences	Provides human primary cells	✓ Eliminates species differences which can make results irrelevant for human patients
Animal testing has ethical issues	Animals not used	✓ Organ-chips can reduce and hopefully eventually eliminate animal testing
Spheroids are hard to make uniform, which hinders reproducibility of results	Can be mass produced	✓ Better ability for reproducibility of results
Organoids lack vasculature	Can mimic vasculature of organs they model	✓ Modeling of vasculature allows for modeling of nutrient and waste transport

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