Status, Trends, and Challenges in Global Bioentrepreneurship

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Edited by

Moira A. Gunn, Arthur A. Boni,
and Stephen M. Sammut

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Global BioEntrepreneurship–both the term and this inaugural volume of peer–reviewed contributions–has a very simple premise: All bioenterprise is global, or potentially so. Thus, while most bioenterprise starts locally, usually initiated by just a few individuals, who become the co-founders, all biotech products and services have worldwide applicability and potential. This journey to global, this experience of being global, means

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[1] Disclosures: The authors do not have a conflict of interest in this subject matter.

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that every bioenterprise must understand today's landscape of nation-by-nation product and device regulatory systems, what may be acceptable in one geographic location that is not in another, how to be multinational all at once, and more. Thus, every bioenterprise of any size is a part of the global biotech industry, and the experience of every bioentrepreneurial endeavor, no matter the size, and every biotech entrepreneur, and, indeed, every sector of the biotech industry itself is important and essential. Of course, the only constant is change: at the frontiers of science and technology, in the nuanced demands of government policy, in societal attitudes, and the ever-present questions of ethics.

Global Entrepreneurship, or *GBioE*, is intended as a place wherein trusted insights may be found and relevant experiences may be shared. One might ask if such a publication is necessary, given the excellent news coverage of the biotechnology trade press. Certainly, news gathering and dissemination are both valuable and essential, but what we attempt here with GBioE is to bring the voices of the global biotech industry to itself. Its insights are often not news items, but rather experience, analysis and reflection, which can only be gained over time, and with thought and consideration. These are the people who take the risks, who dare to undertake the endeavor, who are willing to share their part in moving this humanity-changing industry forward. Our promise is to vet these contributions, and while not every article may speak to you and your work, some just might prove to be essential in your thinking, in your personal strategies and in your future.

In parallel, we seek also to further develop the academic discipline of Bioentrepreneurship, enabling the formal teaching of biotech industry principles and biotech–specific business concepts in all the various disciplines, which are required for success in bioenterprise. From science to intellectual property to venture capital, finance, multinational expertise, regulatory affairs, information systems, and more. The hope here is to give voice to all the participants in bioenterprise everywhere, with mutual understanding and appreciation.

Finally, we hope that you will consider sharing your own insights. How to do this is detailed at GBioE.com, including the opportunity described in Chapter One.

Moira A. Gunn, Managing Editor
Arthur A. Boni, Editor-at-Large
Stephen M. Sammut, Editor-at-Large

CHAPTER ONE

CALL FOR A CROWDSOURCED BOOK

THE STRUCTURE OF LIFE SCIENCE REVOLUTIONS[1]

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SUMMARY

This article is a call to action for our readers and the global life science community at large. The editors of *Global Bioentrepreneurship (GBioE)* are hereby proposing a crowdsourced discussion and ultimately a book exploring whether Thomas Kuhn's 1962 opus, *The Structure of Scientific Revolutions,* is as relevant to the life sciences as it is to the physical sciences. We propose this exchange of ideas in three phases: 1. Submission of articles or opinion pieces from the readership supporting or disputing the claim that Kuhn's book is relevant to the inquiries of life scientists and the biotechnology industry. 2. If there is sufficient response, continued submissions and publication of articles, opinion pieces and reports that chronicle the events and science that form the current life science revolution will be considered for publication. 3. Curation and editing of the most representative articles into a traditional hard copy and e-book, reflecting the analysis that Kuhn's book truly applies, or where it is unable to address the life science revolution.

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[1] Disclosures: The author does not have a conflict of interest in this subject matter.

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THE LIFE SCIENCES AND THE STRUCTURE OF SCIENTIFIC REVOLUTIONS

When University of Chicago Professor Thomas Kuhn published *The Structure of Scientific Revolutions* in 1962, he probably did not expect his book to become one of the most heavily cited scholarly books in history. Nor did he likely expect that the term he coined–"Paradigm shift"–would enter the popular lexicon as an over-used term to describe even modest changes. Most of us trained in the sciences have a basic familiarity with his work, particularly those in the physical sciences. Kuhn, a physicist and philosopher of science, set about to rationalize the process and history of science by building a case that challenged the traditional view of scientific progress as a linear and cumulative process. He instead highlighted the role of a multiverse of factors, such as social, psychological, and cultural, that mediated the development of scientific knowledge. In the over 60 years since its publication, Kuhn continues to influence the philosophy of science and our conceptualization of scientific change.

WHY DOES KUHN MATTER TO LIFE SCIENCE AND BIOTECHNOLOGY ENTREPRENEURS?

Why would the inaugural issue of a publication focused on global biotechnology entrepreneurship set aside a few electrons to raise the story of Kuhn's work? There is a method to the madness. Entrepreneurship in any field is built on a set of assumptions about the perception and characterization of a costly problem, the ideation of an intervention in the form of a product or service, and a calculation that the entrepreneur's idea of that need and its solution will be embraced by the world. That model characterizes all commercial creativity, including biotechnology and those agents who seek to apply the fundamental molecular discoveries into modes of clinical applicability. The force of the underlying science, particularly over the last century, is so compelling that the siren-song of health needs addressable by the new science is irresistible to creators and investors alike. But not everything that transitions from laboratory to factory floor has the expected impact. Sometimes, it is a matter of imperfections: definition of the underlying problem to be solved, the conjured solution, miscalculation of the need and the enthusiasm to address that need with the proffered product. Sometimes, however, there is no miscalculation. The world resists, perhaps because it is not ready to grapple with the problems at hand–unlikely given the needs in medicine–or *especially* that the science behind the solutions does not fit the modalities of prevailing thought or practice. Entire specialties, standards of care, and communities of practice are built around fundamental frameworks. In such circumstances, the biotechnology entrepreneur must step back and reconfigure what is being offered to scale the wall of resistance.

This brings us back to Thomas Kuhn. His assessment of scientific history, as has been summarized in a seemingly infinite number of student papers, including my own undergraduate papers (in 1969!) from which this is drawn, argues that scientific progress is not a smooth and continuous accumulation of knowledge, but rather occurs through revolutionary insights or "paradigm shifts” which are the dominant scientific frameworks or models that guide research within a particular scientific community. Paradigms consist of shared theories, methods, values, and assumptions that shape scientific inquiry. Famously, the Copernican departure from the Ptolemaic interpretation of the universe is the gold standard of paradigm shifts. Even so, minds took the better part of a century to change their conception of the universe. Eventually, within paradigms, investigators engage in what Kuhn calls “normal science.”

When we function in the realm of normal science, we are working within established mind-sets, epistemologies, and fundamental assumptions to answer questions, some of which are puzzles or anomalies, others of which are questions the size of mountains. Either way, normal science’s mission is to refine and expand the existing knowledge within a paradigm. We are trained to think and work within its boundaries, and our fidelity to that paradigm is ultimately judged by peers who reject it or promulgate it, or practice–at first, skeptically–within the new paradigm.

The life sciences are built on observations just like other sciences. We accumulate data to formulate new theories, or to validate or invalidate our own work or the work of others, i.e., the quest for reproducibility. Or a body of science reaches a point of theoretical blind alleys under the prevailing paradigm or becomes entangled in a reductionism that borders on the ideological. In the course of time, however, there may be an accumulation of frustrating anomalies or discrepancies between observed phenomena and predictions made by the prevailing paradigm. At some point, the anomalies reach a critical mass thus challenging the existing scientific framework. Or else, there is a cataclysmic observation that stuns everyone. Either way, the anomalies can lead to a crisis within the scientific community.

On a global basis, reported anomalies do not go unchallenged. Once again, there is a culture that demands reproducibility. Here Kuhn declares that when the accumulation of anomalies becomes significant and cannot be easily resolved within the existing paradigm, the result may be a scientific revolution. Political revolutions take years or decades to fully resolve, if at all. A scientific revolution occurs when a new paradigm emerges, replacing the old one. This process can take even longer. There may be publications. There may be grants supporting further elucidation. Companies might emerge translating the anomalies into some type of product offering, and clinicians–if they see a way of relieving suffering–will cautiously incorporate the results of the revolution into practice. But this is seldom an immediate affair. The Scientific Revolution represents a shift in the fundamental epistemology, assumptions, concepts, and methods used by scientists in the relevant field. And the revolution in one body of science inevitably spills into others.

Here is where the life sciences can get into some conceptual problems when considering the applicability of Kuhn's analysis to our field. Kuhn himself doubted the applicability of his work to the life sciences. As you will read, that question is the point of this essay and is the basis of its modest proposal.

Kuhn further establishes the notion of *incommensurability* suggesting that paradigms are not easily comparable or measurable. Scientists within one field or especially in different fields work under different sets of assumptions and methods. Scientists may see the world and interpret data in fundamentally different ways. Perhaps abruptly, but most often over extended time, a paradigm shift emerges when a scientific community abandons an old paradigm in favor of a new one. Or, in this author's view, attempts to reconcile or incorporate the "new" into the "old." In either case, the transition is often accompanied by resistance and debate within the scientific community. Outside the scientific community, historically there have been tribunals, excommunications, or burnings at the stake.

We must ponder Kuhn's emphasis that paradigm shifts are not solely based on empirical evidence but also involve changes in perception, values, and beliefs, all of which are subject to absorption and the passage of time. After a paradigm shift, a new period of normal science–a post-revolutionary era–begins under the influence of the new paradigm. Thereafter, scientific advancement occurs within the boundaries of the new paradigm until anomalies and puzzles accumulate once again, potentially leading to another revolution. Or revolutions within revolutions. Or a strained synthesis of the old and the new. Or an elated sense that the new was made inevitable by the old.

GBioE poses this question to you: can *The Structure of Scientific Revolutions* be applied to the life sciences and medicine? Can it be applied to the biotechnology industry? This author offers his evidence in this publication, in Chapter Eight, “In-Depth Analysis: Precision Medicine Represents a Classic Kuhnian Paradigm shift (And That Makes All the Difference for Entrepreneurs)”.

What do you think?

As an experiment, this author asked ChatGPT the question:

> “Can Kuhn's *Structure of Scientific Revolutions* be applied to life sciences and biology?”

It took ChatGPT over a minute to formulate an opinion. This is exactly what it reported on November 15, 2023, when asked that question:

> “Yes, Kuhn's *Structure of Scientific Revolutions* can certainly be applied to the life sciences and biology. Kuhn's work is a seminal contribution to the philosophy of science, and it provides insights into how scientific knowledge progresses and undergoes fundamental shifts.
>
> “In *The Structure of Scientific Revolutions*, Kuhn argued that scientific progress is not a steady, linear accumulation of knowledge but rather a series of paradigm shifts. A paradigm is a set of accepted theories, methodologies, and practices that guide scientific inquiry within a particular scientific community at a given time. According to Kuhn, scientific revolutions occur when anomalies or problems arise within a prevailing paradigm, leading to a crisis that challenges the existing framework. This crisis can lead to the emergence of a new paradigm that offers a different way of understanding and investigating the subject matter.
>
> “In the context of life sciences and biology, Kuhn's framework can be applied to the history of scientific advancements and changes in theories and methodologies.
>
> “**Paradigm Shifts in Biology:** Kuhn argues that scientific fields go through periods of normal science, where researchers work within a well-established paradigm, and revolutionary science, where new paradigms emerge and replace the old ones. In biology, there have been several

paradigm shifts, such as the transition from vitalism to mechanistic views, the discovery of the structure of DNA, and the advent of molecular biology. For example, the shift from the belief in spontaneous generation to the theory of biogenesis in the 19th century can be seen as a scientific revolution within the field of biology. Similarly, the transition from the classical genetics paradigm to the molecular biology paradigm in the mid-20th century marked a significant shift in the understanding of genetics.

"**Scientific Revolutions in Evolutionary Biology:** The field of evolutionary biology has undergone significant paradigm shifts, from the early views of Lamarck to Darwinian natural selection and later developments like the modern synthesis. Each of these shifts represents a change in the prevailing paradigm.

"**Incommensurability:** Kuhn introduces the concept of incommensurability, which refers to the idea that paradigms are so different that they cannot be easily compared. In biology, this can be seen in the shifts between different theoretical frameworks, such as the transition from a focus on genetics to an emphasis on epigenetics.

"**Community Structure:** Kuhn emphasizes the importance of scientific communities in accepting and maintaining paradigms. In biology, different subfields may have their own paradigms and communities, and the acceptance of new ideas often depends on the reception within these communities. He emphasized the role of scientific communities and their shared commitment to a particular paradigm, which can influence the acceptance or rejection of new ideas and theories. The life sciences and biology have their own scientific communities, with established norms, peer-review processes, and disciplinary boundaries, all of which contribute to the formation and evolution of paradigms within these fields.

"**Anomalies and Crises:** Kuhn discusses the role of anomalies and crises in the development of science. In biology, anomalies could be phenomena that do not fit within the current paradigm, leading to a crisis that may eventually result in the emergence of a new paradigm.

"However, it's important to note that Kuhn's framework has been the subject of various critiques and debates within the philosophy of science. Some argue that his concept of paradigms is too vague and subject to interpretation, while others question the existence of clear-cut revolutions in scientific progress. Nonetheless, Kuhn's work continues to be influential and provides a valuable lens for understanding the dynamics of scientific knowledge in the life sciences and biology."

Thus, doth the world of Artificial Intelligence opine on the relevance of Kuhn to the life science.

It is important to note that while Kuhn's ideas have been influential, they are not universally accepted, and there is ongoing debate about the applicability of his model to different scientific disciplines. Some critics argue that Kuhn's model oversimplifies the complex and multifaceted nature of scientific progress. Nonetheless, many scholars find his framework a useful and thought-provoking lens through which to examine the history and development of scientific fields, including the life sciences and biology.

Are you persuaded (or offended) by this burst of Artificial Intelligence, that there is an argument to be had and a case, one way or the other, to be made that we are the product of a structural life science revolution and that we are living and working through to the next revolution? If so, *GBioE* proposes to the life science and biotechnology entrepreneurial communities that we generate a "crowdsourced" series of articles, and perhaps a book, collecting those articles in the future, and exploring these questions in three phases:

Phase 1

During 2025, *GBioE* invites anyone to submit an article or an essay arguing one way or another that Kuhn's theory can be applied to the life sciences. The articles will then be subject to an open debate within *GBioE* and perhaps other on-line forums. If the consensus is that the theory does not apply, we will declare the revolution dissolved, we will identify why. If the consensus is that the theory does apply and there is enough enthusiasm in chronicling the ancient, medieval, modern, and contemporary evidence and history of life science revolutions, we will move to the next Phase.

Phase 2

While a good historian of science could have spent the last century researching, interviewing and distilling the work of Nobel Laureates, National Academy Members, leaders of laboratories–both academic and commercial, and others in the life sciences on their work or their perception of where the work of their mentors, themselves and their students or post docs factored into the history of the life sciences and a contribution to the structure of life science revolutions, that would still be the work of one person. Instead, in this age of unbounded exchange, cross-fertilization, and crowdsourced good works, if Phase 1 above leads to the conclusion that there is a story that must be chronicled, captured, and disseminated, then the pages of *GBioE* will be a venue for publication of the essays, research papers, or other opinion pieces on the subject. In particular, as the evidence accumulates (or not) our mission is to relate a newly formulated *Structure of Life Science Revolutions* to the incorporation of science into clinical practice and the products brought to us by biotechnology entrepreneurs and their scientific patrons.

Phase 3

If after sufficient accumulation of contributions and exchange of thoughts and insights, there is a basis and justification for a traditional book*, GBioE* will bring together the best pieces into a coherent narrative in the form of a book. We won't speculate on what that will look like, but it will be the product of editorial work and curation on a continuous basis.

In Conclusion

To put a finer point on making the case, this author refers you to the aforementioned article in this inaugural issue of *GBioE.* It argues that precision medicine represents the trailing end of a structural revolution that began in the 1940s, and that may take many decades more to fully reach a point of full integration into medical practice. That in itself has implications for biotech entrepreneurs. As a bonus, the piece includes a historical perspective from ancient times to the present to serve as an illustration to prospective authors who wish to take up the challenge of contributing to Phase 1.

HOW TO PARTICIPATE

If you are interested in participating as an author of a research paper, essay, opinion piece or other contribution to Phase 1, please contact:

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Chapter Two

BioTech Nation Focus

Can You Rewire Your Brain? A New Frontier for Biotech[1]

Moira A. Gunn, PhD
Host and Executive Producer
BioTech Nation

The biotech industry is seriously interested in the human brain.

In 2024,

- Over 10,000 human clinical trials are underway addressing depression or major depressive disorder (MDD) (Namiot, 2024)
- There are 127 Alzheimer's drugs being tested across 164 human clinical trials (Cummings, 2024)
- NIH's National Institute of Mental Health (NIMH) identifies 35 clinical trials currently in recruitment studying schizophrenia (NIMH, 2024)
- The ALS Association by itself is supporting 149 active research projects in 13 countries (ALS Association, 2024)

Following the relevant literature, scanning clinical trials news and financial markets reports, and listening to scientists speak on neuro-related conditions, the approaches can to seem merge altogether. Phrases which repeat include "crossing the blood brain barrier", or "we've found a new receptor", or "we've identified a new gene target", and these can be hard

[1] Disclosures: *BioTech Nation (BTN)* is a regular interview segment within the one-hour weekly *Tech Nation* public radio program, airing on NPR Affiliates in the US and other public radio outlets internationally. *BTN* interviews are available from multiple podcast outlets, as well as directly from www.biotechnation.com.

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to distinguish, much less remember. Even those which utilize the word *novel* may turn out to be *not-so-novel* after all, when what is different is a slight adjustment to norm.

Most promising is when the term *first in class* is used, where the effort is a genuinely new way to treat a medical condition. Thus, this BioTech Nation Focus centers around the 2024 BTN interview with Dr. Peter Vanderklish, the Chief Scientific Officer of Spinogenix, a privately-held biotech company in San Diego, California (Gunn, 2024). Conceptually, what Spinogenix is trying to do is quite simple … reverse synapse loss in the brain. From the perspective of Spinogenix, a complement of these neuro-medical conditions can be directly traced back to synapse loss. So, the challenge becomes: Can we generate new synapses? When Dr. Vanderklish points to such actual, spontaneous activity in nature, all documented in science, it's not so far-fetched.

Dr. Vanderklish's first point encompasses a number of medical conditions: "Depression, schizophrenia, Alzheimer's, ALS – from the outside, they all look different to us, and yet they all share loss of synapses. But how are they different from each other? If we look at it through the lens of synapses at a basic level, one of the main differences is that you're losing synapses *in different regions* [of the brain].

"In your brain with *Alzheimer's*, what you would be seeing is a pattern of synapse loss that is occurring predominantly, at first, in the hippocampus. and then spreading to other regions, [such as the neuronal cortex, which is involved in memory formation]. In a disease like *ALS*, which is a motor neuron disease, you're going to see synapse loss primarily in the motor cortex. And in disease like *schizophrenia* and *frontotemporal dementia*, you're going to see a pattern of synapse loss that mostly involves the frontal and prefrontal cortical regions.

"In *Depression*, it turns out that you're losing synapses to a degree in some of those same regions, in the hippocampus and the prefrontal cortex. Those are particularly important areas for not just memory formation, but emotional regulation and stress regulation."

This leads to Spinogenix's approach – regenerating synapses, hopefully in those regions where they have been declining. Dr. Vanderklish continues, "We're pursuing synaptic regeneration as a therapeutic approach to address the larger set of what we call the *synaptopathies*. All these diseases have a common loss of synapses. Our compounds are geared towards regenerating a special type of synapse called *glutamatergic synapses*. They are amino acid glutamate, a neurotransmitter, the dominant, most abundant type of synapses in your brain. We think by regenerating synapses through a mechanism that is – to a degree – disease agnostic, you can actually offset synapse loss in these different diseases in different areas of the brain, and hopefully slow, *maybe possibly reverse*, the course of symptoms in different diseases."

It's a commonly-held nothing that as we age, our brain cells, our synapses decline. But is there was any evidence that we can regenerate synapses? Dr. Vanderklish began his response by describing synapses. "Synapses are physical connections between neurons that allow them to communicate with each other. Every neuron has potentially thousands of synapses and can link up with many other neurons by virtue of having many contacts with other neurons. So, neurons link up into large networks of neurons, and it's the synaptic communication between them that allows them to do things like information processing.

"Synapses are really, an indispensable element of your nervous system and are involved in everything you do, everything you think, everything you perceive, everything you say. And, of course, they're involved in memory formation, which is perhaps the most important faculty of mind over a lifetime.

"On average, the human brain has about 85,000,000,000 neurons. And the estimates of the number of synapses that you have range from about a 150,000,000,000,000 all the way up to pushing towards 1 quadrillion. So that's an enormous number."

As for regenerating synapses, "In your adult life, you do have *synaptogenesis*. It's not just a downward curve the whole time. You're at a stable plateau for quite a while. You're losing synapses, you're generating synapses, and they're roughly offsetting in most brain regions for a long period of time. So, synaptogenesis and regeneration are alive and well for a lot of your lifetime.

"Now, as you age, a lot of these diseases have too many components to them. They have degenerative processes, obviously, which are very multifactorial. But also with age, you lose the ability to regenerate [synapses], and we think our compound is coming in and coaxing a particular molecular process that is allowing synapses or neurons to sort of wake up, if you will, and to be able to regenerate synapses where they're needed.”

In fact, there are myriad examples throughout nature. “A good example of where this happens in nature is under conditions of stress, [such as] in hibernating animals. There are studies that have been done on hibernating ground squirrels, for instance, where, they [hibernate] because of a scarcity of food. These animals evolved to go into a state where they use less energy, and then you get to survive the winter, as well, so they hibernate. They go into a state of torpor, low body temperature. They lower their metabolic rate all in an effort to sort of survive the stresses of winter and low intake of food. Now this is a big challenge for the brain, which is very metabolically active. One of the things that the brain does is to retract some of its synapses.

“These studies in ground squirrels are very interesting because, when they go into *hibernation*, it turns out that *their brains actually show evidence of Alzheimer's like changes*. They develop *tangles of tau*, the hyper-phosphorylated tau protein that you see in the Alzheimer's brain. They lose some of their synapses. And yet within hours after coming out of the hibernating state, their *synaptic density* comes back to normal. The percentage of synapses that they've lost has returned to a normal state.

“Also, some of the Alzheimer's like changes that you see in their brains are reversed. So, there is this ability to have the brain rebound and regenerate after states of severe metabolic stress, which is a component to neurodegenerative disease, and to do so in short order and in an appropriate way.

“Interestingly as well is the fact that in hibernation, the additional studies were showing that memories that were encoded in ground squirrels shortly *before* hibernation actually remained intact *after* hibernation. There could be a lot to explain that. One of the explanations could be that even though some of the synapses have been lost, when synapses were regenerated, they were regenerated at the right level and in the right places.”

Dr. Vanderklish also addressed the frequently referenced topic of the amyloid plaque theory of Alzheimer’s disease. “The amyloid theory of Alzheimer's disease, in its most basic form, posits that the generation of a small protein fragment called amyloid beta is a central player in the pathogenesis (initiation) of the disease and accounts for most of the pathology and the symptoms that you see. It's thought that this short protein fragment is toxic to both synapses and neurons, and it increases inflammation, and does other things. *It's a decent theory but, you know, it may be wrong* … I do think it can be safely concluded that amyloid beta is at least a stressor on neurons and synapses. It may not be the central player in the disease progression, but it's not something you want a lot of in your brain. I think probably the bigger problem with the amyloid theory is that *it's just insufficient*."

Spinogenix is currently conducting multiple Phase 2 trials with their lead compound, SBG 302. It is a small molecule, which is ultimately intended to be formulated into a pill, and is taken by mouth on a daily basis. In simple terms, it is intended to get into the subject's brain where it would work to regenerate synapses with "the potential to slow or potentially even reverse, some of the symptoms of these diseases". Four independent Phase 2 trials are underway to address specific disease conditions: Alzheimer's, ALS, schizophrenia, and Fragile X syndrome.

Also important is the emergence of improved technologies to evaluate clinical trial endpoints. A number of non-invasive techniques can now make precise measures of neurophysiological readings, such as increases in density of synapses and neurodegeneration. These include improved EEG's and transcranial magnetic stimulation (TMS). Besides ameliorating some of the well-known disadvantages of patient reports and subjective measures of functionality, the existence of this technically-generated data enables the potential for earlier and more accurate readouts.

Yet even with successful trials, Dr. Vanderklish would be the first to point out that many open questions will remain. "We [already] have data speaking to the fact that when we regenerate synapses in the absence of any underlying disease process in preclinical models. We see that they persist. They can actually persist for weeks or more. Now it's anybody's guess how that persistence is going to change in the context of one Alzheimer's patient versus another, in Alzheimer's versus ALS, in frontotemporal dementia versus [any of] those, etc.

"That's not something you can really adequately model in preclinical studies, and we're just going to have to find out in the clinic. But for right now, we think we can do benefit without doing harm with once daily dosing. We may find out later that you don't have to take it all the time."

More information about Spinogenix can be found at www.spinogenix.com. The full BioTech Nation interview with Dr. Peter Vanderklish is available at www.biotechnation.com.

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CHAPTER THREE

AN ASSESSMENT OF THE PROPOSED EU PHARMACEUTICAL REFORMS ON INDUSTRY[1]

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OVERVIEW

Background

The European Union (EU) is one of the world's most novel experiments in political and social governance. It boasts 27 nations or Member States (MS) ranging from economic powerhouses like Germany to former Soviet satellite states such as Hungary. Since the EU's birth in 1993, the Union has progressively shifted towards greater integration, including with the healthcare systems of its Member States. Europe's biopharmaceutical industry has participated in this shift, particularly with the creation of the European Medicines Agency (EMA) in 1995. As espoused in its founding charter, the EMA was established "to harmonize the work of existing national medicine regulatory bodies" (EMA, n.d.-b).

Since then, the EMA's jurisdiction has grown to rival that of the US Food and Drug Administration (FDA). Along with small molecule drugs, the EMA has evolved to evaluate complex biologics, advanced gene therapies, and combination therapies, among other innovative therapeutics (EMA, n.d.-b).

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[1] Disclosures: The author does not have a conflict of interest in this subject matter.

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Despite the EMA's growth and centralization of authority, the European Commission, the EU's executive branch, has uncovered significant health inequities in Member State access to novel therapeutics.

> "Innovative and promising therapies do not always reach the patient, so patients in the EU still have different levels of access to medicines." (European Union, n.d.) (European Commission, 2020).

The European Federation of Pharmaceutical Industries and Associations (EFPIA), which represents biopharma interests in the EU, contextualized this inequity in a 2022 market access survey, reporting that

> "on average, a new medicine will reach patients fastest in Germany in 128 days; this compares with 918 days in Romania and 1,351 days in Malta with a European average of 517 days." (EFPIA, n.d.).

The group's findings provide new evidence for a longstanding observation that Northern and Western European countries have better access to innovative medicines than their Southern and Eastern peers (EFPIA, n.d.).

To address these historical disparities, the European Commission launched a multi-prong policy initiative in 2020 entitled *Pharmaceutical Strategy for Europe* (henceforth referred to as the "Strategy" in this paper) (European Commission, 2020). This biopharmaceutical initiative is built on four pillars that can be disaggregated into: (1) access to affordable medicines, (2) competition & innovation, (3) crisis preparedness & response, and (4) enhancing global competitiveness (European Commission, 2020). Guided by these pillars, the European Commission released a package of proposed pharmaceutical reforms in April 2023, which European lawmakers call "the largest reform in 20 years" (European Commission, 2023a).

EXCLUSIVITY REFORMS

Overview

At a top line, the proposed reforms reduce the baseline years of exclusivity but create opportunities to earn more years than is currently available. In today's regulatory regime, a medicine with a market authorization—a permit for a drug to be distributed and sold across the EU—has 10 years of exclusivity, of which eight years is awarded as *data exclusivity* or *regulatory data protection* and the remaining two years are called *market exclusivity*. The EMA defines regulatory data protection as the time:

> "during which the marketing authorization holder benefits from the exclusive rights to the results of the preclinical tests and clinical trials on the medicine. After this period, the marketing authorization holder is obliged to release this information to companies wishing to develop generic versions of the medicine." (EMA, n.d.-a).

In contrast, the EMA considers market exclusivity to be:

> "when similar medicines for the same indication cannot be placed on the market." (EMA, n.d.-c).

In practice, the EMA will wait for the reference drug's regulatory data protection to expire, it will then evaluate a generic for a market authorization, but the generic will remain commercially unavailable until the reference drug's market exclusivity lapses. The Strategy's proposed reforms slash the eight years of regulatory data protection to six years while preserving the two years of market exclusivity. This would then provide innovative drugs a total of eight years of exclusivity, a drop from 10 years. (See Table 1 for summary.)

Policy Objective

This reform aims to accelerate the market entry of lower-cost generics and biosimilars to further the Strategy's goal of increased access to affordable medicines across the EU. Unlike the US where generics account for about 90% of filled prescriptions, just 67% or approximately two-thirds of filled prescriptions are generics (Howey, 2023). EU lawmakers hope that lower-cost alternatives to reference products will particularly benefit Eastern Member States (MS) where incomes tend to be lower than rest of the EU.

Table 1. Baseline Exclusivity

Current Exclusivity Provision	Proposed Exclusivity Provision	Change
8 years of regulatory data protection	6 years of regulatory data protection	Loss of 2 years
2 years of market exclusivity	2 years of market exclusivity	No change
10 total years of exclusivity	**8 total years of exclusivity**	**Decrease of 2 years**

Industry Mitigation Strategies

In response to the reduction in exclusivity, biopharmaceutical firms might employ a number of strategies to mitigate their revenue losses. Some innovator companies might resort to pay-for-delay or pay-for-limited launch which the European Commission describes as an arrangement in which:

> "an original pharmaceutical manufacturer pays generics products to stay out of the market" or specific markets (European Commission, 2016).

Other innovator companies might introduce their own authorized generics or biosimilars which are:

> "product[s] that [are] exactly identical to a brand name drug but marketed as a generic version without the label of brand on it." (Latwal, 2021).

Some innovator firms might delay launching their drug until they have attained approval for the largest patient population. Biopharma companies will likely employ or develop additional strategies that accelerate their climb to peak revenue. Partly due to these regulatory changes, the European Federation of Pharmaceutical Industries and Associations (EFPIA) has asserted:

> "long-term access to medical breakthroughs in Europe will be harmed." (EFPIA, 2023).

ADDITIONAL OPPORTUNITIES TO EARN EXCLUSIVITY

Two Years for Extra Regulatory Data Protection for Supplying All 27 Member States

In anticipation of such pushback, the European Commission included provisions enabling biopharma firms to earn additional years of regulatory data protection. One of the most notable proposals offers biopharma firms two extra years of regulatory data protection if they can make their drug available to all 27 Member States within two years of receiving a market authorization. Like the Commission's desire to expedite generics, the driving force behind this proposal appears to be a desire to ameliorate the access disparities noted in the Strategy. Some will likely question the feasibility of this proposal as Member States have varying timetables in making pricing and reimbursement decisions for approved drugs, which ultimately dictate market entry and access. Germany and Malta can represent two illustrative cases; Germany takes an average of 128 days to make a pricing and reimbursement decision whereas Malta can up to 1,351 days, or nearly four years (EFPIA, n.d.).

To align countries to the same schedule, the European Commission has proposed several mechanisms. Starting in 2025, all Member States will use a joint health technology assessment, a tool used to evaluate the "added value of new medicines and medical devices" (European Commission, 2023c) (European Commission, 2018). In theory, the joint health technology assessment will expedite pricing and reimbursement decisions among developing Member States, who often lack the resources and expertise to take quick action. Additionally, it will benefit biopharma companies by reducing their administrative burden as they will not need to file a health technology assessment with each Member State. If a firm meets its obligations under this proposed framework but a Member State fails to uphold its duties, a drug company can request the Member State to issue a waiver so the company may qualify for the two extra years of regulatory data protection. Any Member State that receives a waiver request must respond within 60 days; otherwise, the biopharma firm's waiver automatically goes into effect (Blaine, 2023). Even with these guardrails in place, some Member States might leverage or withhold the waiver to seek additional financial concessions from a drug manufacturer.

One Extra Year of Regulatory Data Protection for Additional Indication that Advances the Standard of Care

A cornerstone of the Strategy is promoting innovation and making the EU a global biopharma hub. Buried in the European Commission's reforms is a proposal that enables innovative firms to earn an additional year of regulatory data protection if their drug provides a significant clinical benefit for an additional indication over the existing standard of care. The biopharma industry is anticipated to be lukewarm to this proposal. For starters, Member States can have different standards of care for the same condition. Resolving these differences will require the EMA or the European Commission to standardize clinical guidelines across the continent, which is no easy feat given the differences in medical expertise, access to resources, and culture, among other factors. Furthermore, the European Commission has not spelled out what constitutes a significant clinical benefit and what metrics might be used to make this assessment. It is possible the joint health technology assessment, launching in 2025, will be employed to address this question. Nevertheless, this proposal will likely operate in tandem with another regulatory data protection opportunity.

Six Additional Months of Regulatory Data Protection for Comparator Trials

Innovator firms can gain an additional six months of regulatory data protection if they complete a head-to-head trial against a "relevant and evidence-based comparator." (Blaine, 2023). In some cases, the comparator will likely be the standard of care such as an advance line of cancer therapy. Combining this policy with an extra year from advancing the standard of care, drug makers could theoretically earn a year-and-half worth of regulatory data protection from one appropriately designed study. In practice, biopharma companies will likely eschew this policy given their historic opposition to head-to-head research (Mundy, 2009). Drug makers have criticized such studies in part because patients and providers might perceive the "losing drug" as suboptimal, leading to financial losses for the drug company. In addition, the losing drug maker might suffer reputational harm from such a trial, potentially reducing the company's market value. If a company chooses to pursue this pathway, it might encounter patient recruitment challenges. Namely, patients might not want to participate as they view any treatment short of the standard of care as suboptimal. This provision faces a number of implementation and operational headwinds, particularly in attracting enough companies, patients and researchers.

Six Additional Months of Regulatory Data Protection for Unmet Medical Need or Orphan Designation

Like the previous provision, biopharma entities can earn six months of regulatory data protection if their product addresses unmet medical need or is considered an orphan product. The European Commission defines an *unmet medical need* as:

> "a condition for which there exists no satisfactory method of diagnosis, prevention or treatment in the Union or, even if such a method exists, in relation to which the medicinal product concerned will be of major therapeutic advantage to those affected." (Stokx, 2019).

Additionally, the European Commission considers an *orphan disease* to "life-threatening or very serious conditions that affect no more than 5 in 10,000 people in the European Union." (European Commission, n.d.-a)

To win this bonus, some companies might develop indications for very small patient populations, such as ultra-rare diseases. This drug development strategy might increase the number of orphan designations awarded by the EMA, which already jumped from 17 approved orphan products in 2021 to 21 such medicines in 2022 (Kamerikar, 2023) (Schofield, 2023). Such a market shift could benefit the EU rare disease community, wherein 95% of the known 7,000 rare diseases lack therapeutic options (European Commission, 2020). On the other hand, patient advocates may criticize this provision as orphan designations have often been linked to higher drug prices, a countercurrent to the Strategy's objectives. EU policymakers, consequently, will need to balance the Strategy's aim of innovation with access, an all too familiar intrinsic tension to health policy.

Table 2 summarizes the Regulatory Data Protection time awarded for each of these exclusivity opportunities.

Table 2. RDP Bonuses for Non-Orphan Drugs

Description of Bonus	Time Awarded
Address an unmet medical need	6 months
Conduct comparative clinical trials	6 months
Treat a new indication that provides significant clinical benefit	1 year
Enter and supply all 27 Member States with the drug	2 years

EMA APPROVAL TIMES

Background

Historically, some industry analysts have asserted that the EU's pharmaceutical review and approval system delays access to treatments, which ultimately drives up costs for patients. Industry associations, such as the European Federation of Pharmaceutical Industries and Associations, have added that the proposed reforms will exacerbate this trend, with EFPIA's Director General, Nathalie Moll, most recently saying:

> "We have gone from being at the forefront of discovering new treatments to being well behind the U.S. and if current trends continue, then by 2030 Europe will be eclipsed by China." (Moll, 2023).

These critics often back their claims by comparing the EMA to its American peer, the US Food and Drug Administration (FDA). A 2022 study assessing the median approval time for oncology treatments found the FDA took 241 days whereas the EMA lagged behind at 426 days (Clinical Trials Arena, 2022). Part of this difference is attributable to the finding that 72% of oncology treatments were first filed with the FDA, about a median of 20 days before the EMA (Clinical Trials Arena, 2022). Even after accounting this for difference, the EMA is still nearly five and half months behind its American counterpart.

Proposed Reforms

To address this shortcoming, the European Commission's proposed reforms seek to accelerate the EMA's two-step approval procedure. Currently, the EMA's:

> "Committee for Medicinal Products for Human Use (CHMP) perform[s] a scientific evaluation and [then] the European Commission issu[es] an approval." (Clinical Trials Arena, 2022).

The Committee for Medicinal Products's assessment takes 210 "active days" which constitute the time the EMA devotes to conducting a scientific assessment of the drug candidate (EMA, 2023). Active days are different than calendar days in that active days do not account for pauses in the regulatory process, during which the review stops to allow the drug company to respond to the committee's questions. After a thumbs up from the panel, the European Commission has 67 days to grant a marketing authorization (EMA, 2023). The proposed reforms cut the EMA's 210 active days to 180 days and slash the European Commission's time allowance for granting marketing authorization to 46 days (European Commission, 2023b).

If these reforms are implemented, it could make EMA review times more comparable to the FDA. As a result, companies might then choose to file FDA and EMA applications simultaneously, helping to achieve the Strategy's principles of access and equity. Additionally, the expedited timelines could increase the EU's attractiveness as a biopharmaceutical research and development destination, accelerating innovative therapeutics