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RESEARCH ARTICLE

Seeking Life Science Innovation Opportunities and Beyond: The Art of Blending Science, Medicine, and Business

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ABSTRACT

This update on life science innovation extends Boni's 2018 works[1,2] to include industry stakeholder expert opinion. This paper's focus is to address three research questions relevant to innovation within the biopharmaceutical industry concerning 1) its current state, 2) challenges, opportunities, and frameworks, and 3) existing examples in the extant literature and practice relevant to progress and challenges. It utilizes mixed methods involving a 1) narrative review to establish a current understanding of the extant literature and frameworks and 2) qualitative interviews to coalesce themes around the core research questions. The first section summarizes current industry challenges, successes, and best practices that support sustained and disruptive innovation in the biopharma industry. It charts a brief overview of proven models for innovation, entrepreneurial thinking, and for development of open innovation as applied to this complex, challenging, continuously evolving industry. This initial discussion advocates the pursuit of commercialization that 1) incorporates a phased, interdisciplinary, collaborative approach and 2) blends the principles of business, science, and technology through diverse, collaborative teams, networks, and alliances. The paper transitions to a second section. This effort builds on these concepts and provides insights and alternative perspectives from a cohort of leading experts within the biomedical investment, development, and commercialization space. It also illustrates and leverages collective intelligence through interdisciplinary perspectives across the life science landscape and reinforces trends for pursuing innovation.

Keywords: Biopharma, Digital health, Entrepreneurial thinking, Innovation, Life sciences, MedTech, Open innovation, Pharma 4.0, Triple chasm

INTRODUCTION

Healthcare globally faces many challenges. Multiple systematic shocks are driving change in its needs and delivery. Such elements include economic, political, technological, and social drivers. The biopharmaceutical industry is not immune to these considerations, so firms must evolve and innovate in their technological offerings, commercialization processes, and business models to survive and thrive. Hence, this paper examines the evolution that is moving the industry into a new era. It seeks to explore the advances in "the art" of blending science and business through a collaborative framework that leads to scalable, sustainable innovation within this unique, challenging, and regulated global industry.

The genesis for this narrative emerges from Boni's[1, 2] and U'Prichard's[3] foundational works, with the latter pioneering the concept of "informed drug discovery and commercialization" to include creative partnering of academia, emerging companies, and pharma to accelerate the pace and success of drug development.[3] These contributions [1, 3] emphasize the convergence of science with the interdisciplinary collaboration of diverse teams to commercialize the emerging technologies associated with the biopharmaceutical and medical device industries.[1, 4, 5]

This paper's focus is to address the following research questions:

1. What is the current state of innovation within biopharma?
2. What challenges, opportunities, and frameworks exist relative to innovation?
3. What examples exist in the literature and practice to illustrate progress and challenges?

This exploration of these questions employs a mixed methods approach, including a narrative review initially and qualitative interviews of thought leaders and practitioners subsequently.

This initial discussion supports the premise that the successful commercialization of advances by the biopharma industry requires a parallel, balanced, and informed coupling of business and technology. It observes the accelerated evolution of "the industry business model" through global alliances, partnerships, and networks coupled with well-developed local ecosystems and clusters. Such convergence and collaboration provide a collective intelligence accelerated thru global alliances across the value chain leading to clinical and breakthrough technological advancements (e.g., Coronavirus Disease 2019 (COVID-19) ribonucleic acid (RNA)-based vaccines, gene therapy, clinical progress in rare diseases, gene editing, clustered regularly interspaced short palindromic repeats (CRISPR), robotics, artificial intelligence (AI), and digital radiology) to serve compelling and significant medical needs.[6] However, within these times of advancement come challenges that the industry needs to address to deliver its breakthroughs. Most notably, these relate to affordability, access, equity, public perception, and restrictive public policy.

This paper's second part extends this discussion and adds to a comprehensive collective intelligence and understanding of the topic of innovation in biopharma and the research questions posed as part of this manuscript's objective. Given the importance of pursuing an interdisciplinary and collaborative approach, we include this section to provide perspectives beyond our own, including venture capital (VC), clinical development, consulting, and commercialization. Such discussion reinforces the power of interdisciplinary collaboration and collective intelligence, highlights best practices, and explores innovation challenges.

These two sections illuminate the evolving model for biopharmaceutical innovation. Accordingly, this discussion includes extant theories (or models), a framework, and real-world perspectives from practitioners and stakeholders in the ecosystem. These considerations help chart the course for the industry's evolution thru leveraging the technological, process, and business model innovations to address market and societal needs. By embracing such factors, the industry can continue to deliver access and value to all stakeholders across the healthcare delivery value chain.

METHODS

This paper utilizes a mixed-methods approach to address these guiding questions. Part 1 utilizes a narrative review to gather and analyze relevant contributions that define the extant literature and frameworks applicable to biopharma innovation. This section elaborates on how the literature evolved and fashions a conceptual framework.

Part 2 utilizes qualitative methods. This effort involved interviewers presenting the three core questions to eight biopharmaceutical thought leaders and practitioners (consulting, company executive leader and investors) to gain “real world” perspectives on these areas. Analysis used qualitative techniques. These efforts focused on coalescing key themes based on the three core questions and thought leader responses. Interviewee verbatims provide support and offer perspective from each interviewee.

SECTION ONE - GENERAL OVERVIEW OF THE TOPIC OF INNOVATION

For success at the firm level, the biopharma community recognizes and leverages the importance of the broader innovation ecosystem available for the entity to efficiently "rent" parts of the value chain outside its boundaries. This statement is consistent with the findings of the Massachusetts Institute of Technology's (MIT's) Stakeholder Framework for Building and Accelerating Innovation Ecosystems (Budden & Murray, 2019). For innovation theories, refer to the works of Christensen and colleagues' "Disruptive Innovation" [8] and "The Innovators Prescription, A Disruptive Solution for Healthcare" [9]; to Kim and Mauborgne's "Blue Ocean Strategy" [10]; and to Verganti's "Design Driven Innovation."[11] These contributions stand out among the multiple overlapping innovation models at the firm level. Design thinking is an important innovation approach to incorporate into these frameworks (and is discussed later). Ulwick's "Outcome-Driven Innovation"[12] views the development of products and services in the context of filling user needs with outcomes that incorporate products and services that allow them to address their "jobs to be done"[13] with appropriate outcomes. Understanding "the job" is essential to developing appropriate and compelling solutions (i.e., products and/or services).[12,13] The market is defined as the job, the executor(s), and the context. While other models exist, these stand out to us "as classics" and are well worth studying. Technology firms and executives have applied them routinely; however, life science professionals have limited use of these approaches. Accordingly, these approaches provide a good background for technology, scientific, clinical, regulatory, and commercialization professionals.

More recently, Phadke and Vyakarnam[14] have offered the triple chasm model to extend Moore and McKenna's "Crossing the Chasm" [15] and Roger's original work on "the diffusion of innovation."[16,17] Phadke and Vyakarnam[14] base their model on years of research involving data from 300 firms across multiple verticals. Within this construct, they observe three significant transitions that firms need to address for commercial success with their innovations. Chasm I involves moving from a concept to a working prototype. Then, Chasm II involves moving from an early to a fully functional product or service with a sustainable business model. Finally, Chasm III (unicorns) involves scaling from early customers to the main body of customers. Interestingly, the 1st working session of our annual Biotechnology Innovation Organization (BIO) Entrepreneurship Bootcamp used analogous descriptions for emerging products and business models in utilizing screening metaphors for business evaluation, characterizing the different maturity stages as Project, Product, and Platform, with the ultimate goal of reaching the latter state.[18]

These "theories" are well-stated and proven through observations. Thus, they are statements of causality. Scientists, technologists, and business development specialists comprising innovation teams in the biopharma industry are accustomed to using "hypotheses" (in parallel with physical, biological, and chemical principles) as guides in proceeding through the drug development process from laboratory to an approved product using a "target product profile" (TPP).[19–21] The United States (US) Food and Drug Administration (FDA) advocates this approach for firms to proceed through clinical testing phases and to engage in broader adoption in the post-approval market stage.[21] In the business and entrepreneurial world, these "theories or models" from the literature can be useful to guide behavior and decision-making regarding business model development and evolution in the market.

We view these "innovation models" as lenses through which "the world" is viewed to enable predictions, hypotheses, or forecasts to be made. However, they may also act as "blinders", limiting one's ability to identify what might not fit into our existing models. According to the famous statistician George Box, "essentially, all models (theories) are wrong, but some are useful."[22] Therefore, we recommend using these innovation theories or principles more as "pattern recognition methodologies" and not as rigorous theories, algorithms, or models that predict physical or chemical phenomena. Box[22] also observed that Occam's Razor[23,24] guides individuals toward the simplest description to describe the pattern. When two descriptions may be used to explain the same phenomena, the simplest generally works best, and they are easier to understand, apply, and validate through observations.

Concerning observation as a methodology, Christensen and colleagues[8] identified and validated five components of "the innovator's DNA." These include associative thinking, questioning, observing, experimenting, and networking. Such behaviors and approaches are essential to innovation teams.

Of course, those in the biomedical space should proceed through a parallel set of technology and business model validations using the previously discussed models and methods. On the biopharma business model side, multiple stakeholders validate product/market fit (P/MF)[25,2], which this paper will discuss later. These actors, or "P's," include patients, providers, physicians, payers, and partners.[27] There is a 6th P: the public and their policy-making representatives.[5, 27] Accordingly, healthcare is not "just one customer or user profile and value proposition." Instead, it involves multiple value propositions and

constraints due to the existence of these different stakeholders.

Therefore, throughout the product development journey, teams of scientists, entrepreneurs, and innovators should utilize the simplest description to achieve a minimum viable product (MVP).[28] They must also be satisfied with the ability to experiment, recognize, and use patterns (or screens) to guide the iterative product development/market fit at each innovation process stage.[29, 30] The lean startup model or methodology embodies such an approach.[5, 28, 31] It is an insightful utilization of Popper's[32] scientific method approach to discover needs, solutions, and product/market fit through iterative experimenting and learning. Therefore, Biopharma/ MedTech/Digital Health teams should be well-versed in this methodology. The "fake it until you make it" strategy that Carreyrou[33] describes within "the technology world" and Silicon Valley, such as seen with Theranos, does not apply in healthcare.[34] Thus, the position that "science can become a business" does exist. However, it occurs when the principles are applied appropriately, legally, and ethically thru diverse high-performance teams and led by enlightened and ethical leadership!

Identifying and recognizing patterns is a key outcome for any of these models and approaches. Therefore, an approach that "taps into" the collective intelligence of a diverse team is essential. Martin's "The Design of Business"[35] knowledge funnel illustrates this collective understanding and predictability. He framed this funnel that starts with a state of "mystery, chaos, or lack of any explanation."[35] Teams then gain clarity and understanding by proceeding down this funnel. Accompanying this effort, they should apply Christensen and colleagues' "Innovator's DNA" five principles of observation, questioning, experimentation, networking, and associative thinking.[8] Accordingly, these teams will progress to an understanding where some rational explanations appear. This process leads to identifying patterns, screens, or heuristics that can be applied to the product or process commercialization.[36–40] The final stage of evolution occurs at the end of the funnel. Further analysis leads to an outcome and potentially the development of an ability to predict outcomes accurately.[35]

Christensen and colleagues[9] focus on disruptive innovation within healthcare. They frame disruptive innovation similarly where experts (e.g., highly trained surgeons or "drug discovery specialists") are required at the earliest stage since these professionals are trained to see patterns to guide their 'jobs to be done.[9] However, less trained individuals and potentially machine learning (ML) algorithms (less expensive and good enough solutions for certain jobs) can progressively displace (or disrupt as predictability becomes possible) these professionals.[9] These authors continue their narrative by illustrating healthcare system disruptions along two dimensions: 1) Migrate the provider: Expensive specialists → less skilled practitioners → self-care; and 2) Migrate the point of care for disease treatment: Teaching hospitals → general hospitals → outpatient clinics → homecare.

Thus, they observe that opportunities for innovation exist along both of these dimensions as technology evolves and business models are developed and validated to exploit and deliver those technology-based solutions.

Biopharma is now applying previously discussed innovation models, guidelines, and principles. Such practice is leading to the emergence of opportunities originating in multiple areas. Noteworthy examples are emerging in digital health, personalized medicine, the ability to edit genes (e. g., CRISPR), and the use of RNA to develop vaccines for corona virus-19 (COVID-19) (e.g., Moderna and Pfizer/BioNTech.[5, 41, 42] Invention and emergence of these revolutionary technologies are "ripe for commercialization" when coupled with multidisciplinary teams "ultra-focused on the market, and investors and executives able to manage risks to compete in a capital-efficient mode. All of these efforts are executed while such firms navigate high levels of government involvement (e. g., regulatory approvals, intellectual property) and negotiated reimbursement for products to assure end users benefit from these technological advances. This journey is not a simple process to implement and manage; it also requires leadership and collaboration of multidisciplinary teams located across sites across the globe and working remotely (especially noteworthy during COVID-19). Such efforts reflect a true demonstration of the power of collective intelligence and collaboration.

BIOPHARMA INDUSTRY EVOLUTION PATHWAY

Historically, technologies ranging from small-molecule discovery and development to the emergence of biotechnology, gene-based technologies, and currently on to the holy grail – the "ever-promised" personalized medicine – and the use of artificial intelligence (AI) have enabled the biopharmaceutical industry. The business model continues to evolve parallel with the pursuit to create, deliver, and capture value. As the industry matures, its challenges are two-fold. The first is to be technologically enabled. Next is to earn a profit (even if some of the returns are shared with partners through the principle of "rent sharing" through partnerships). This mode of operation has and will remain as the

industry evolves. Balancing risky technological advances with financial affordability and accessibility is challenging but expensive.

The consulting firm Ernst and Young (E&Y) provides an overview of the "state of the industry" in its highly-read annual report.[43] Its industry examination highlights three stages of business model evolution: Pharma 1.0, Pharma 2.0, and Pharma 3.0 (and now to Pharma 4.0, as discussed below).[43]

In the Pharma 1.0 era, therapeutics were generally small, organic molecules with high market potential. The business model was termed the "blockbuster drug" era (i.e., using the term to describe the potential "billion-dollar molecule") that could be used to sustain the organization across its period of market exclusivity and, made possible largely thru creating strong national and international patents (and their creative extensions).[43, 44]

The transition to Pharma 2.0 and biotechnology began in the 1980s, as the signals of decline in the 1.0 era included patent cliffs, research and development (R&D) productivity challenges, globalization, pricing, reimbursement, and regulatory issues (this latter driver of change persists to this day).[43, 45] During this era, biotechnology began to evolve as a science. This business segment, based largely on venture capital (VC)-backed early-stage companies, was much more entrepreneurial in its approach to drug development and financing strategies. "Nimble biotechs" evolved, so partnering became more prevalent as the larger pharma companies and their labs found potential innovations in the universities and national labs. Small, agile companies need funding, clinical testing abilities, and market access. Thus, scientific advances in discovery drove this era as the industry emerged with the advent of protein-based therapies, genomics, and associated technologies. Then there were predictions regarding the "coming of personalized medicine," with the caveat emptor almost there! Nevertheless, the life cycle for innovation in biopharma is much longer than for technology companies – and, understandably, adding technology into the mix thru AI and robotics adds even more complexity.

The next era, in the 1990s and early 2000s-time frame, focused on new, internally developed technologies. However, pharma engaged these via open innovation partnerships with emerging companies and established pharma partners.[46, 47] Mergers and acquisition efforts drove considerable consolidation of the pharma and biotech industries. This activity led to the era termed "biopharma," where the larger firms can now appropriately bring both small molecule and biotech-based products to market to solve the healthcare problems of the world population.[48]

E&Y characterized the Pharma 3.0 era as "healthy outcomes."[43] This period observed a shift from a physician and provider-centric model to one where consumers and payers have emerged with more power in the ecosystem. While innovation is driven by technological evolution, adoption is constrained by affordability. The idea of health outcomes focuses on wellness and prevention. Also, it facilitates the earliest stages of personalized medicine to move from the innovators and early adopters closer to mainstream markets. Glen Giovannetti, one of the principal authors of E&Y's "Beyond Borders," observed, "in this capital-constrained environment, the industry can no longer afford inefficiency and duplication in drug research and development."[43] The industry must remove duplication, encourage pre-competitive collaboration, pool data, and let researchers learn in real-time."[43]

Such principles utilizing this "outside-in" approach will be extended to include MedTech, robotics, and the evolving digital medicine/health field. Digital transformation is now accelerating and leading to a convergence of where healthcare, traditional biopharma, and technology (the tech industry) collaborate as the industry moves to a customer and user-centric business model (i. e., Pharma 4.0).[49–51]

Moving to a variation on a theme, this paper's primary author – an innovator, serial entrepreneur, and professor – has experienced and advocated the use of design thinking and service design as an inherent customer (or user) centric methodology. There will be many ways to incorporate design thinking into organizational culture and in the quest to provide an exceptional user experience for services associated with healthcare and its delivery. Boni and Foley's recent work[52] illustrates this observation by highlighting the challenges and approaches to satisfying is industry's "multiple P's" needs.

The biopharma industry segments alluded to above represent a very significant part of the value chain of the broader HealthCare industry, which in the US accounts for more than ~$2 trillion of expense, or about 17.5% of US gross domestic product (GDP) (and growing) according to Burns' "The Business of Healthcare Innovation."[53] The US continues to "lead the pack" in the race to the highest cost of health care. Thus, cost containment, affordability, and risk management remain ever-present challenges.

Drug/pharmaceutical product portfolios change over time as needs change, patents expire, and science evolves, leading to new solutions to diseases and disorders. So, "what is coming next" beyond pharmaceuticals and the inevitable emergence of digital health? Such innovations include: 1)

more drug/device combinations; 2) non-hospital based telemonitoring, telemedicine, even 'mobile medicine'; 3) digital radiology (already here), digital pathology (emerging), virtual colonoscopies (in development); 4) targeted diagnostics (therapeutics); and 4) convergence of devices and drugs (e.g., stents, implants [orthopedic – spines, knees, hips]).

THE EMERGENCE OF A BROADER DIGITAL HEALTH CONVERGENCE AND TRANSFORMATION

The emergence of digital medicine (or digital health) promises to transform and disrupt healthcare over the next several decades. This movement provides unique and interdisciplinary challenges. Rising to these challenges, as Editor in Chief of the *Journal of Commercial Biotechnology*, the primary author worked with colleagues at the University of California, San Diego (UCSD), to organize and host a symposium on emerging opportunities in Digital Health offered "digitally" in December 2021.[54] This issue highlights several essential business model components discussed in this paper and equally applies to innovation in cross-industry segments.

Accomplishing this digital transformation requires broader cross-industry collaboration and convergence around one common set of goals – affordable and available healthcare that creates value for all parties, including patients, providers, physicians, payers, partners – and now – the public. This symposium's essential message is that the emergence of digital medicine transformation will progressively transform and disrupt healthcare over the next several decades. In the technology industry, digital and mobile technology has changed our lives over the last two decades thru the internet, search, social media, etc. Accomplishing this transformation in healthcare will require cross-industry collaboration and convergence around a common goal: affordable and available healthcare that creates value for all parties (as noted in the prior discussion).

For further information on emerging technologies, the authors encourage readers to examine the Frost and Sullivan report[55] on business model transformation in health care and the highlights from the 2021 UCSD Digital Health Symposium.[54] A few extracts of "what's coming next" include: 1) robots to assist autistic children; 2) drug delivery patches, ingestible sensors and devices to assist with medication adherence, virtual colonoscopies, robotic surgeries, teleradiology/pathology, etc.); 3) brain-computer interface applications to connect the visually challenged → wearable electronics, sensor fusion, energy harvesting; 4) next-generation connected care for continuous and personalized care; and 5) augmented/reality-based surgery – real-time information sharing during surgery ("everything as a service" business model, which is a take-off from the software as a service cloud-based model popular in the tech space).

This discussion also points to further insights into this dynamic in articles by this paper's lead author and colleagues (Joseph and Moehle).[46, 56, 57] The first involves a focus on creative value sharing along the value chain with academic and commercial partners (open innovation as opposed to vertical integration). This effort should employ creative partnerships and consortia to create a networked innovation model for creating, delivering, capturing, and sharing value. It should leverage academia, emerging companies, and industry to form extended teams across the value chain. Relevant examples include the fully integrated pharmaceutical network (FIP Net) concept developed by Eli Lilly[58] and the consortium approach pursued by Pure Tech Ventures in creating the Enlight Biosciences model[59] in partnership with multiple biopharma tech companies. These examples involve the use of "stage appropriate" financing vehicles for translating thru each stage of commercialization from the laboratory to the clinic to commercial product (service) – government, private equity (angel, angel consortia, VC, and private equity), and public funding. They use the concept of "bio-dollars" (milestone-based payments that progress as risk is reduced along the path to market) as an integral part of the financial deal structure to balance risk and reward. Also, these efforts use public-private partnerships to finance higher risk, early-stage investments and enhance downstream partnerships. Examples include various ab initio formation of platform companies utilizing breakthrough technologies by Rock Health (e.g., Foundation Medicine)[60] and the Harrington Project that couples academic medicine to BioMotiv to accelerate discoveries to the market leading to breakthrough medicines.[61] This innovation came by guiding these companies thru Phases 1 and 2, facilitating partnerships between these emerging companies upon successful completion of Phase 2, and transitioning into the Phase 3 stage and beyond through pharma partnership and collaboration.

Essential to this effort is developing and growing "seasoned" management teams with expertise and network access across the value chain to match technology with market needs. Such can engage the utilization of virtual management teams that can add value to a portfolio of opportunities and with the expertise and ability to cross the "valley of death" from the inspiration and ideation phase of innovation thru the execution phase to commercialization. This approach may require developing and adopting new management skills

(collective intelligence) and processes to manage these open and virtual teams that span the globe.

Another strategy involves the adoption of networked "accelerators" to move seamlessly thru the commercialization pathway (translational research to cross multiple "valleys of death" from the laboratory, thru clinical testing, to FDA approval and the marketplace).[46] Examples include Johnson and Johnson's Innovation's JLabs, California Institute for Quantitative Biosciences (QB3), and Rock Health.

Closing this section, Boni and Moehle[57] summarize the following principles for startups and emerging companies. First, operate lean and use agile development processes. One can accomplish this objective by keeping the cost of capital low while addressing product/market fit and scaling team business and technology expertise adaptively as the market develops. Second, use creative financing via for-profit and not-for-profit sources and partnerships. Third, create and grow innovation teams. This effort involves the development of collaborative and diverse interdisciplinary teams, which evolve thru the commercialization phases when scaling from startup to "platform company" to market. However, while this piece is essential, some of the "DNA" embedded at the earliest stages must persist.

CONCLUDING DISCUSSION

This paper offers a "short list" that illustrates the challenges regarding the blending of technology and business that impacts the future of medicine and health. Technology includes AI and machine learning (ML), machine vision (MV), big data, robotics, digital devices, and low-cost genomics. On the biotechnology side, we would include synthetic biology, gene editing, CRISPR, regenerative medicine, and the "just-on-the-horizon" personalized medicine.

Nevertheless, this discussion would be remiss if it did not include multiple significant hurdles to progress. Such considerations include intellectual property, regulatory, and, most significantly, access/reimbursement/pricing issues. Healthcare innovation is a complex challenge and perhaps a challenge for a subsequent publication. Also, new insights into this topic should extend beyond academic literature and include practitioner publications (e.g., *Harvard Business Review*, *Sloan Management Review*, *Pharmaceutical Executive*), business journals (e.g., *Fortune*), and books. For example, Boni and colleagues recently wrote several book reviews for the *Journal of Commercial Biotechnology*. Each discusses issues that relate to the evolution and current challenges faced in the industry.

"Why Startups Fail: New Roadmap for Entrepreneurial Success" by Harvard professor Tom Eisenmann[62, 63] involves a multi-case study of early-stage companies that succeeded vs. those that failed. He found that the extended team and its leadership are the most important predictors of success for an entrepreneurial venture. This finding highlighted that leadership based on teams, partnerships, alliances and networks were important success factors in all industries. Such attributes embody dynamic capabilities by offering a means to create and sustain a competitive advantage to commercialize, bring innovations to market, and fulfill unmet needs.[64]

Eisenmann's book prompted a "deeper dive" into the essential components needed for success to build, grow, lead, and sustain innovative organizations of any size – from startups through their emergent growth stages and to maturity.

This insight encouraged further exploration of additional materials to complement Eisenmann's book and is summarized in "Keys for Building and Leading Teams for Innovation: Three book reviews and author commentaries."[65] This multi-book review examined three outstanding contributions to the literature: 1) George White: "The Mystery of Organizational Collective Intelligence – a key to survival in a competitive world"[66]; 2) Kevin Bethune's "Reimagining Design: Unlocking Strategic Innovation"[67]; and 3) Mikel Mangold, "Today's Superpower: Building Networks."[68]

Briefly, these 2022 publications provide insights into unlocking strategic innovation in cross-industry organizations: one deals with the concept of organizational collective intelligence;[66] the second with incorporating design thinking and service design into the organizational culture;[67] and the third focuses on building and leveraging networks and alliances.[68] These three book reviews include short, focused, moderated question-and-answer format exchanges with the respective authors.[65]

It would be remiss not to include an excellent book by Walter Isaacson, titled "The Code Breaker: Jennifer Doudna Gene Editing and the Future of the Human Race."[69] This book focuses on the story of Jennifer Doudna and her quest to develop and commercialize clustered, regularly interspaced short palindromic repeats (CRISPR), a revolutionary gene editing technology.[69]

Finally, and in closing, there is Gary Pisano's classic book "Science Business: The Promise, the Reality, and the Future of Biotech."[70] When Pisano wrote this book, many questioned whether biotech would meet its promises. Since then, the critical learning is that new business models (discussed previously) consisting of alliances and collaborations – the Pharma 4.0 model – led to these technologies'

development and commercialization. The rapid development of COVID-19 diagnostics, vaccines, and therapeutics provides excellent examples. What has been learned over time was how the industry structure, or anatomy, borrowed from Silicon Valley (tech), presents some "flaws" when applied to biotech – or at least has some serious challenges. The first challenge involves the uncertainty inherent in human biology and processes leading to very high technology risk profiles since it is difficult, time-consuming, and expensive to predict that the technology will "work." Recall that only 1 of 10,000 initial drug candidates gets to market with FDA approval.[71] The capital intensity and development life cycles are much higher and longer, so partnerships between emerging and established organizations are needed. The next consideration, complicated and overlapping intellectual property (IP), exacerbates the problem since patents with strong freedom to operate are essential (refer to the Code Breaker book noted above). The third issue involves more complicated business model challenges, which consider "multiple P's" or stakeholders. It is a much more complex set of dynamics for bringing products to market and getting paid with sufficient return on investment. Finally, harnessing and leveraging collective and cumulative (institutional) learning is a huge and expensive challenge in the Pharma 4.0 domain. What is next involves chasing the promise of personalized medicine and perhaps even AI and digital health via cross-industry partnerships.

AN "END-NOTE" FOR PROSPECTIVE BIOENTREPRENEURS

Several "takeaways" that might help emerging bioentrepreneurs have been included in a recent symposium's proceedings organized by Boni and colleagues at the University of California, San Diego (UCSD).[4, 63] The following "top ten" points summarize essential steps from these contributions and apply to biotech, MedTech, and digitally-enabled companies.

Boni's "Top Ten" iterative steps to guide and build successful companies

1. Employ the **Entrepreneurial Process Model** of the late Jeffrey Timmons, Ph.D., as one proceeds (e.g., opportunity, resources, team, and leadership).[72] **Leadership** identifies the **opportunity**, acquires the **resources** needed to develop and validate the opportunity, balances the **tranches** of **funding** incrementally timed as risk is reduced **(value inflection points)**, and builds a diverse and collaborative **team**, including partnerships and alliances.
2. Recognize that opportunities are validated by **engaging and observing users, customers, partners, and competitors** to identify potential entry and growth opportunities and solutions capable of creating change and adding significant value to all parties in the healthcare ecosystem (e. g., **patients, physicians, providers, payers, partners,** and the public).
3. Innovators need to "**get out of the building" to develop the MVP and Business Model Canvas – see no. 8)!**[73–75] It is important to have the perspective of all the players in the ecosystem - interact, understand, and adapt! Focus on the user and patient centricity first, demonstrate that the MVP works, then engage other players.
4. Focus on developing **a platform solution** vs. a single-product solution to pursue these opportunities. Platforms are designed to leverage extended networks and to be scalable as markets evolve and are proven.
5. Build and expand a **diverse entrepreneurial team** that: 1) identifies and validates opportunities; 2) acts under enlightened and active leadership; and 3) uses a lean, entrepreneurial approach to reduce risk incrementally and create value sequentially. This lean or agile approach leads to the identification of an appropriate **MVP and Market Entry Point (MEP)** – that can be scaled later as the market and solutions evolve.
6. Leverage fundamental, proven entrepreneurial methodologies and frameworks that have evolved and been validated over the last several decades in other fields of innovation (e.g., Disruptive Innovation from Christensen; Blue Ocean Strategy from Mauborgne and Kim; Design Driven Innovation from Roberto Verganti; and the Business Model Canvas of Osterwalder.[8, 10, 11] All can be used to align and validate key components of business models in digital health.
7. Utilize the definition of **The Market** articulated by Tony Ulwick in terms of "Jobs to be Done" (JTBD).[12, 13] Since the entrepreneur often creates a solution for a new market that does not yet exist, it is defined not as "how many devices or solutions are or could be sold," but as follows: **Market = JTBD + Executors + Context. Specific solutions to market needs** change over time as the market is created and evolves with improvements to the entry product. The challenge for the entrepreneurial team is to identify needs (JTBD) that are unmet, poorly met, or met by expensive and/or inconvenient current solutions. Also, recognizing that while jobs are functional, they may also have **social and emotional components** that may be important to

users. This insight suggests implementing a design thinking/service design approach.[52]

8. It is also important for the entrepreneurial team to implement a milestone-based commercialization strategy that drives product evolution and market penetration and to validate the **nine elements of the Business Model Canvas (BMC)** of Osterwalder[75] – **Customer Facing side**: customer segments, value propositions, channels, customer relations, revenue streams: **Company Facing side**: key resources, key activities, key partnerships, cost structure.
9. Understand the value propositions and **"motivators to adopt" by all parties in the ecosystem**. Such considerations include **1) less expensive; 2) "get the job done better;" 3) easier to use; 4) easier to buy; 5) faster, and 6) more convenient.**[76, 77] These can be on the business-to-consumer and business-to-business side Osterwalder[76, 77]. Do not forget the **emotional and social considerations** that can be equally important and more difficult to understand.
10. Finally, expand **the platform** since it is designed to be scalable, used to create sustainable value and leverage networks that one can augment over time with **partnerships and alliances** across the value chain.

In particular, two "uber-strategies" rise to the top of this paper's list:

1. Seek to build scalable platforms. Single products may serve market entry but building a sustainable and scalable business requires thinking bigger and building a technology-enabled platform. Refer to the recent paper by Yuanxin (Sheen) Rong[78] on the "power of building technology-enabled platforms" and some excellent examples in biopharma via mini-case studies on Millennium, Alnylam, Moderna, and Kymera.

2. Strive to build partnerships early and often. Boni and Joseph[46] developed a four-model framework for corporate innovation. Their paper identifies four models for organizations to pursue simultaneous core growth and transformation leveraging open innovation principles: 1) corporate accelerators — engage with or create autonomous startups; 2) external startup platforms — engage with startups through established third parties; 3) consortia or alliances — leverage resources of peers and emergent players across the innovation ecosystem; and 4) direct entrepreneurial approach — work from within the organization to develop new units.[46] This work identifies "innovation maturity" as the key factor in selecting the most appropriate model for the organization.[46] Additional considerations include the organization's resources, processes, and values (RPV) and the developmental status of the transformative technology.[46] Finally, this discussion highlights that model choice(s) are dynamic and can evolve as the organization's innovation capacitates and adapts to change.[46]

While technology is both important and essential, it takes much more than an interesting, breakthrough technology to solve the problems and challenges of 21st biopharma! A recent IQVIA (formerly Quintiles and IMS Health, Inc.) Institute statement signals the continuing challenge: "issues of disparities in medicine access and pricing are a continuing area of focus for the global community, with the World Health Organization (WHO) leading discussions around fair pricing through their Fair Pricing Forums, most recently held in 2021."[79]

SECTION TWO – FROM CONCEPT TO PRACTICE: INSIGHTS FROM LEADING INDUSTRY EXPERTS, INVESTORS, AND PRACTITIONERS

INTRODUCTION

Part one of this paper highlights the importance of interdisciplinary collaboration and collective intelligence in blending science and business to accomplish scalable and sustainable innovation. This section builds on these themes by engaging practical perspectives and expert opinions from multiple life science stakeholders on pharmaceutical innovation, challenges, and future paths. These individual experts included Laxminarayan Bhat, Ph.D. (Chief Executive Officer, Reviva Pharmaceuticals), Douglas Crawford, Ph.D. (Managing Partner, Mission BioCapital), Dennis Gross, Ph.D. (Chief Executive Officer, the Pennsylvania Drug Discovery Institute), Peter C. Goughnour, Ph.D. (Director, JD Biosciences), Gregory Horowitt (Co-founder and Managing Director of T2 Venture Capital), Dr. Thanigavelan Jambulingam, Ph.D. (Professor, Saint Joseph's University), Uday Phadke, Ph.D. (Co-founder and Chief Executive Officer, Triple Chasm Company), and Sharon Watling, Pharm.D. (Principal, Watling Clinical Development). Their perspectives include VC, clinical development, marketing, and consulting. Their opinions highlight the need for and benefit of utilizing a collaborative approach to innovation in the life sciences. The following is a synthesis of the conversations centered around three core questions.

1. What is your take on the current state of innovation (product, process, and business model) in pharmaceutical life sciences?
2. What are the major challenges that are impeding progress?
3. What do you see as good examples that illustrate progress?

What is your take on the current state of innovation (product, process, and business model) in pharmaceutical life sciences?

Product

According to Horowitt, innovation is always a back-end metric. It is never a front-end metric. The state of innovation is only measured once the offering touches the market because the consumers or the market either adopt it or does not. Therefore, it is hard to know internally if the product will be innovative externally. There are always many novel inventions in the pharmaceutical industry because scientists are constantly experimenting and trying new things. The industry has made profound improvements in patient care through therapeutics and the convergence of technology and drugs. Dr. Jambulingam also notes how the convergence of technology and our understanding of diseases allows us to find therapeutic solutions for patients. He explained, "Patients do not need drugs. They need solutions."

According to Dr. Watling, there has been a considerable amount of innovation in the products, specifically in cell therapies, gene-based therapies, and the human microbiome. Products with mechanisms of action and technologies that were once unimaginable are now becoming the standard of care. Dr. Jambulingham also thinks the innovation is good in terms of the product. "Companies are striving to bring new products to market. We saw products quickly brought to market within a year due to COVID-19."

According to Dr. Phadke, while the industry has come a long way and is on an important pivot, it has a long way to go. Unfortunately, the timing will be longer than most think. For example, gene therapies have come a long way, but fundamental science still needs to be understood.

Process

Dr. Gross elaborated on an article he read in 2020. He explained that the piece described how the industry was "constantly innovating. He added that this piece highlighted that if the environment was not right for innovation, what is the point? Gross continued that there is more that goes into the innovation process than actual innovation. The industry needs to consider the perceptions of the innovation; will it be adopted? Is the innovation deployable; can it be used in low-tech environments? How will the innovation integrate into local medical and health practices? Are companies looking at the right populations and thinking enough about health disparities? Patent protection is another thing to consider.

According to Dr. Watling, there has been a noticeable shift in the process. Some examples include 1) shifts from paper case report forms to all electronic case report forms; and 2) a decentralized clinical trial, where the sites come to the patients rather than the patients having to go to the site. Another recent example involves how many rare-disease-focused companies enhance the recruitment and retention of patients in clinical trials by going into their homes and taking the transportation burden off their shoulders.

Dr. Phadke offered a relevant closing comment that is an excellent takeaway. He observed that there had been a significant change in drug discovery, specifically in how new biological compounds are synthesized in translational medicine and applied to new treatments.

Business Model

On a macro level, Dr. Jambulingam highlighted that the current industry business models have been changing. He explained that the industry was primarily a small molecule business, then biologics emerged, moving to the new space of cell and gene therapy. He stated, "We used to have volume-based or scale-based business models, but these do not apply to the new market." New models are evolving to be value or outcome-based, and Dr. Jambulingam concludes that we will see more of this evolution in the future.

From a micro level, "there are important changes to the architecture of the pharmaceutical industry which have occurred in the last 20 years," explained Dr. Crawford about the disaggregation of the pharmaceutical industry. The industry evolved from a vertically integrated structure-where most products came from internal research and development- to one where most products have been externally acquired. This profound change has been healthy for the industry as it has facilitated the creation of more exploratory companies. "Another change," according to Dr. Crawford, "has been the growth of contract research organizations." These organizations provide access to services only available inside a pharmaceutical company. This external capability has allowed tiny companies to compete equally with the largest companies. Mission BioCapital (MBC) Biolabs has contributed to this evolution since it changed how much capital was required to begin lab operations. "People can produce experiments in the first week rather than in the ten or more months it would take to acquire the needed capital and permits," he explained.

According to Dr. Watling, there has been a shift from big pharmaceutical companies with their in-house R&D groups to biotech hubs where many small companies are conducting early research activities. These small companies start with venture capital and other fundraising modes to foster early product development, hoping to be acquired by or partner with a big pharmaceutical company to perform the Phase 3 trials and eventual

commercialization. There is less internal R&D in big pharma and a lot less "in-house" clinical operations because they outsource it to clinical research organizations (CROs) and partner with emerging companies. This industry is changing very quickly with a considerable amount of consolidation, particularly CROs.

A final piece is conducting early trials in other countries. Dr. Goughnour highlighted the strategic decision of his firm to conduct first-in-human studies (phase 1a-c) in Australia due to cost savings, less bureaucracy, and incentives to incorporate. Dr. Bhat echoed this point and noted that similar incentives exist for conducting early-stage trials in the Netherlands. He noted, "running the study ex-US in Australia or the Netherlands can provide us data quickly for moving into phase 2 in the US and perhaps save us money and time related to longer-term animal toxicity work."

What are some examples of innovation challenges?

The US Inflation Reduction Act of 2022 has the potential to exert significant pressure regarding drug pricing. Dr. Jambulingam explained, "This legislation will impact the industry, especially with top-selling drugs. For the industry to survive, they need to create efficiency in everything they do." He added, "Payers cannot cover everything, and if your technology is not chosen, you are not reimbursed." This pharmaceutical management professor noted, "That is why firms need to understand what they are bringing to market early; They should have a plan early on showing how you will commercialize the drug."

Dr. Jambulingam also asserted, "The research and development engine is traditional and expensive… making success high risk. There is no guarantee that the outcome will be successful every time a company goes through the research and development process." Dr. Crawford queried. "How do you redesign your innovation engine to reduce costs, increase speed to market, and go through regulatory hurdles faster?" He added, "The fundamental productivity of the industry and cost of clinical development was challenging to the innovation progress."

Another challenge Dr. Crawford saw was the gap between talented people with cool ideas and successful companies. When he and his team opened their first incubator in 2007, $750 million in annual federal funds went to basic biomedical research at the University of California, San Francisco (UCSF), but only between two to four companies per year were emerging from the university. He observed, "That was a terrible return on investment for society. At the end of the day, fundamental research should lead to better treatments for patients." He and his team postulated that part of the issue restricting those ideas from coming out of academic labs was the "zero-to-one startup" difficulty. They built incubators and accelerators to help academic labs and startups "make it better, faster, and cheaper to start companies."

Dr. Jambulingam identified a similar gap in human capital. He noted, "People are retiring fast, so a large gap in skill and talent is coming." This professor added that there is an estimate saying around 100,000 employees are needed in the industry, and more are needed in healthcare delivery. He queried, "How are we going to fill these gaps? We have no idea, and companies are constantly spinning off. Is that paying off?"

Dr. Jambulingam continued the conversation by discussing a challenge facing clinical trials. He observed, "We do not have a lot of diverse participants. Minorities and other ethnicities are not well represented. Their response behavior could be different, and the United States is very diverse. Making technology fully applicable to the whole population would be difficult without adequate representation."

Dr. Gross offered a similar perspective. He shared the example of articles claiming that oxygen pulse oximeters could overestimate oxygen saturation in darker patients, leading to increased death rates. This phenomenon would lead to another problem identified by Dr. Gross. This executive observed, "Innovative, disruptive technology may be creating more problems than it's solving." Technology isn't the answer to everything. He added, "the problem is we fall in love with technology and perhaps oversell some of our breakthroughs."

As the conversation continued, Dr. Gross offered, "Another challenge is most patients are not being informed properly… especially as technology gets more sophisticated. Are the support groups, nurses, physicians, and others involved with deploying the technology ready to do so? He added, "I do not think we are doing a good job of looking at the entire continuum from bench to bedside to community, and that needs to be addressed. We do not have good explainers to communicate how these drugs and technologies work, and people do not believe what the industry tells them." In addition to better communication with patients, another area to consider is countering misinformation. Dr. Gross observed, "This challenge offers a good opportunity for strategic partnerships. The US is at an interesting tipping point for industry and public health."

Dr. Watling stated that identifying the appropriate clinical endpoint of a trial is still a challenge for the pharmaceutical industry. For example,

the registration endpoint for autism is irritability, but patients don't care about that as much. Therefore, there is a need to bridge the gap between what could be more likely to achieve regulatory approval versus identifying an objective, reproducible endpoint that is meaningful to patients.

According to Horowitt, one of the big challenges is having leadership that understands the importance of investing and creating an environment where that innovation has every chance to survive because it is impossible to make innovation happen. Only the chances of it happening can be increased. In mature systems, governing the constraints makes sense because there is a defined output. However, creating a system can encourage the right behaviors when people do not know what is known or unknown.

What are examples of progress?

Dr. Crawford observed, "the expansion of research and therapeutic modalities has been a big change, providing many tools to both the discovery and treatment stages." He continued explaining how the creation of Genentech is an unsung innovation regarding the incredibly creative and sophisticated ways of securing capital. This venture capitalist underscored, "The creation of Genentech demonstrated how great things emerge from commercially-minded and basic science collaboration. Within the last ten years, public markets and large capital investors have been helpful to the growth of the industry."

Dr. Jambulingam observed, "The establishment of private-public partnerships between companies and the government helps things get done faster. He explained, "We saw this with the COVID vaccines." This professor indicated that more partnerships like this one could be valuable, and another one to consider would be with insurance companies.

According to Dr. Watling, advances in therapeutics are among the most significant examples of innovative progress. For example, there has been a shift from small molecules to replacing missing genes in patients who are missing a gene.

Dr. Phadke shared his perspective on the mixture of public-sector and private funding. The funding model is extremely important because there is a lot of money and capital. But the question lies in the motivation for that capital. Therefore, government entities, big pharmaceutical companies, and smaller companies need to align their interests and make strides in innovation

CONCLUSION

As the biopharmaceutical industry transitions from Pharma 3.0 to Pharma 4.0, this paper's authors and the interviewed experts see continuing opportunities for interdisciplinary collaboration to overcome disruptive and sustained innovation challenges. The current state of innovation does provide a healthy problem-solving environment. The industry has realized significant strides in the products being developed and offered, enabled by cutting-edge technology advances in gene and cell therapies. The product development process has become much more efficient and has progressed from "trucks full of paper forms" to all electronic forms secured on the cloud. The ongoing digital transformation exemplifies this transition. The industry business model has also advanced. It has fostered an environment where various entities are willing to take risks that enable innovative therapies to shape the standard of care from translational medicine to clinical development, regulatory affairs, and commercialization.

As it stands, new and diverse products, evolving business models, and a shift in focus of processes to become more patient-centric have laid the groundwork for strategic partnerships and innovation thru collaboration. Evidence exists that various stakeholders (e.g., established biopharma firms, biotech startups, incubators, accelerators, academia, consulting firms, clinical research organizations, venture capital, and government entities) work together to advance patient care. We are seeing strong evidence that collective intelligence is becoming more prevalent. While the industry is capital-intensive due to its complexity, collaboration demonstrates successful new products enabled by continued progress on new products based on emerging technologies. Thus, all stakeholders must align their motivations to enable efficient strategic collaboration to address current and future diseases, treatment advances, and administrative and economic challenges (and opportunities).

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