Blockchain in Pharmaceutical Research and the Pharmaceutical Value Chain

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Abstract Pharmaceutical research can yield life-changing agents for treating and curing disease, improving quality of life, extending life, and enhancing innovation in the broader healthcare ecosystem. However, the historical processes and approaches for drug discovery and development are fraught with high costs, low success rates, and enduring challenges—from preclinical research to Phase IV surveillance. Overall, the pharmaceutical value chain, consisting of (1) research and discovery, (2) clinical development, (3) manufacturing and supply chain, (4) launch and commercial considerations, and (5) monitoring and health records, suffers from pain points at a variety of stages across multiple vector types. The strengths and characteristics of distributed ledger technology (DLT) (e.g., blockchain), in conjunction with other established and emerging technologies, map extraordinarily well to many of the most substantial challenges in pharmaceutical research and the pharmaceutical value chain. This chapter outlines contemporary and future blockchain-integrated solutions to accelerate and optimize drug discovery and development pathways. It also explores key opportunities well-aligned with blockchain for the five main categories of the pharmaceutical value chain. Finally, this chapter debunks the misconception that technical challenges are the chief obstacle for the conception and implementation of blockchain-based solutions in the pharmaceutical industry while alerting the reader to other challenges and approaches to navigate them.

Keywords Blockchain · Drug discovery · Distributed ledger technology · Pharmaceutical research · Pharmaceutical value chain · Supply chain

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1 Brief Overview of Pharmaceutical Research

1.1 Drug Delivery and Discovery

Taking a therapeutic from a concept to a marketed drug molecule is an extensive process that typically requires a decade or more of research and costs more than $2 billion to complete [1]. The process begins with target identification, where basic research is conducted to identify a biological entity (e.g., gene, signaling molecule, etc.) associated with a particular disease that can be modulated by a small molecule or biologic (i.e., a "druggable" target) [2]. Once a druggable target has been identified, the target must undergo a series of tests to confirm that regulation of the target is associated with modification of the disease state, which typically includes the use of in vitro studies and animal models of the disease. In the next stage, compounds are identified that can modulate the target's activity, which in many cases can include hundreds or even thousands of molecules to be screened using assays designed to detect target engagement. Compounds exhibiting target engagement are then subjected to additional screening to identify a single "lead" compound or a few lead compounds possessing drug-like characteristics such as high potency and selectivity, aqueous solubility, and metabolic stability. The final stage in what is considered to be the discovery phase of the drug discovery and development process is lead optimization, where the structure of the lead compound(s) is/are modified to increase the safety and efficacy of the drug by improving properties such as off-target binding or oral absorption [3]. The discovery stage alone takes 1–3 years and $200 million on average to complete [2].

Following the discovery phase is a period of preclinical development, which involves extensive animal testing to further evaluate the safety and efficacy of the drug prior to advancement into clinical trials. These studies are required by the United States Food & Drug Administration (FDA) and provide critical information regarding the potential for the drug to successfully progress through clinical trials [1]. An additional 1–2 years and $100 million or more are typically required to complete preclinical development studies [2].

While the discovery and preclinical stages of drug development are costly, the clinical trial stage is by far the most costly phase of the entire process, averaging $1–2 billion to complete phase I, II, and III trials [2]. Phase I clinical trials are primarily intended to evaluate the drug's safety and determine an appropriate dose in humans. These studies are typically conducted on healthy individuals and comprise less than 100 participants. Phase II trials further evaluate drug safety, but in this stage, drug efficacy is also evaluated through studies in 100–300 individuals who have the disease state. Phase III trials dive deeper into the safety and efficacy of the drug by evaluating different patient populations, doses, and drug combinations in several hundred to several thousand individuals with the disease. While a phase I trial may only take several months to complete, phase II and III trials typically last several years. Only 12% of drugs successfully progress through phase III trials to receive FDA approval and reach the market [1]. After FDA approval, the safety

and efficacy of the drug continue to be monitored in what is referred to as phase IV. This post-approval monitoring phase provides additional information that may not have become apparent in smaller cohorts of clinical trial subjects, such as adverse events, drug–drug interactions, and necessary dose adjustments in certain patient populations. This final phase generally lasts for several months and can cost an additional several hundred million dollars.

1.2 Challenges Associated with Drug Delivery and Discovery

Numerous challenges exist across all stages of the drug discovery and development process, from the discovery and preclinical phases extending into the clinical trial and post-marketing phases. The nature of these challenges is varied, pertaining to aspects that may be scientific, logistical, financial, ethical, and/or legal. To a large degree, financial challenges associated with drug discovery and development stem from difficulties related to the other stated problem areas (e.g., scientific or logistical issues). Accordingly, the cost of delivering a new drug to market has gradually increased over time, despite major advances in science and technology to enable the potential development of previously unattainable therapies. Consequently, high costs combined with the uncertainty that a drug will successfully reach the market represent a significant barrier to drug development.

1.3 Challenges Associated with Preclinical (i.e., In Vitro, In Vivo) and Phase 0/I–IV Studies

Challenges in drug discovery and development begin with gaps in the science that inform drug discovery efforts [4]. While deficiencies in understanding the pathophysiology of diseases make it difficult to identify drug targets, these deficiencies may not be realized until a drug reaches phase III clinical trials when a drug fails to demonstrate clinical efficacy. Further complicating this dilemma are animal models that insufficiently represent human disease, leading to drugs that demonstrate efficacy in preclinical studies but not in clinical trials. Likewise, animal studies sometimes fail to identify toxicities that arise in humans during clinical studies.

Partly contributing to these gaps in knowledge of disease mechanisms and failures in preclinical to clinical translation are deficiencies in published data [4]. This problem spans all stages of drug discovery and development—from understanding disease pathophysiology to identifying disease biomarkers and drug targets to translating preclinical models into human disease. There are complexities at every step with each of these aspects of drug discovery and development dependent on the reliability and reproducibility of published data.

Both the production and the dissemination of published data have their limitations. For example, deficiencies among both investigators and reviewers in conducting and interpreting statistical analyses can result in the publication of statistically insignificant data. Furthermore, due to the "publish or perish" culture of academia, investigators may be motivated to cut corners or outright falsify data for the sake of publication. Alternatively, the volume of data that can now be generated due to advancements in instrumentation and technology creates complexity in the storage, maintenance, and retrieval of data, potentially leading to innocent mistakes in data conversion, processing, and/or reporting. From a dissemination standpoint, the lack of reporting of raw data and detailed experimental methods can make reproducibility from one lab to another challenging. In addition, because negative results are typically not published, time and resources are likely wasted on studies destined to fail.

Finally, disregarding potential problems with the published data in and of themselves, the sheer volume of published data available makes searching the literature for relevant and comprehensive information an arduous and time-consuming task. Because all publications are not open access, accessibility to published data for some investigators may be limited by cost.

Increased collaboration among academia and the pharmaceutical industry can help remediate some of these challenges by facilitating data sharing, sharing costs, and expanding the pool of expertise contributing to a given drug discovery and development effort [4]. Collaboration between academia and industry is particularly beneficial in bridging the basic biomedical research required for the early stages of drug discovery (i.e., academia) with the costly later stages of drug development (i.e., industry). While academic drug discovery programs can identify drug targets and drive "hit-to-lead" campaigns during the discovery stages, these programs generally have to rely on partnerships with industry to fund and facilitate late-stage preclinical development and, especially, clinical trials. Drug development is also facilitated by those in the academic sector via the provision of consultancy services and in roles like key opinion leaders [5]. However, collaboration creates its own challenges. With expanded collaboration comes increased complexity in the storage, maintenance, retrieval, and, particularly, data sharing due to the introduction of multiple sources of information in physically distanced locations. In addition, as intellectual property (IP) is critical to developing a revenue-generating drug product, the involvement of multiple entities in the discovery and development of a drug introduces an additional layer of complexity to the ownership and protection of IP and the distribution of royalty payments.

Similar challenges arise in the later stages of clinical development (e.g., phase III and IV clinical trials) when more patients and multiple clinical trial centers are typically involved in collecting data. Not only is the storage, maintenance, retrieval, and sharing of data a logistical concern, but with clinical studies, it is also an ethical and legal concern, as the personal information of trial participants must be protected. Furthermore, specific information at times must be blinded to patients and/or investigators to avoid introducing bias into the study. Likewise, prior to initiation of a clinical trial at any stage (phase I–IV), informed consent must be collected from trial participants (generally at multiple locations). This information might also be

shared with auditors and regulatory review boards while maintaining patient privacy. Similarly, "big data" (e.g., medical records, genomic databanks, clinical trial results, etc.) can be a useful source of information across all aspects of the drug discovery and development process, but also come with logistical and ethical/legal challenges regarding collecting, maintaining and distributing these data, as well as protecting the privacy of individuals involved.

1.3.1 Adaptive Trial Design

One strategy developed to improve the efficiency of clinical trials is the implementation of an adaptive trial design. The FDA defines an adaptive trial design as "a clinical trial design that allows for prospectively planned modifications to one or more aspects of the design based on accumulating data from subjects in the trial" [6]. By permitting adjustments to the trial based upon data that were not yet available at the start of the trial, adaptive trial designs can potentially improve statistical efficiency, ethical conduct, data interpretation, and general risk reduction for both trial sponsors and trial participants. However, while an adaptive design has several potential advantages, maintaining trial integrity becomes more challenging when evaluating interim data. Care must be taken to preserve the blinding of investigators and patients intended to remain blinded throughout the study. Regardless, adaptive trial design offers particular promise for personalized/precision medicine and allows for a more rapid response to epidemics due to viruses (e.g., COVID-19, Ebola hemorrhagic fever, Middle Eastern Respiratory Syndrome) [7].

2 Introduction of the End-To-End Pharmaceutical Value Chain

2.1 Five Main Categories: (1) Research and Discovery, (2) Clinical Development, (3) Manufacturing and Supply Chain, (4) Launch and Commercial Considerations, and (5) Monitoring and Health Records

For the purposes of this chapter, the following five phases comprise the pharmaceutical value chain: research and discovery; clinical development; manufacturing and supply chain; launch and commercial considerations; and monitoring and health records [8]. Before delving deeper into each phase, it is critical to understand that each phase serves as a funnel for future phases and that there may be temporal overlap of phases throughout progression down the chain.

As the first phase in the pharmaceutical value chain, **research and discovery** represents a significant challenge. Responsible for the discovery and preliminary

understanding of eligible pharmaceutical compounds, success in this phase is not only required for further progression in the chain but also cyclically relies on and contributes to past and future successes, respectively. The Therapeutic Target Database (TTD), a collection of documented protein and nucleic acid targets, reports that 427,262 potentially active target drug structures have been identified. Additionally, 33,598 have been profiled for potential drug properties, and only 2,797 have successfully become approved drugs [9]. For scope, these numbers are winnowed from the million or more compounds that undergo initial screening [3].

The pain points in the research and discovery phase are fairly easy to identify. Siloed information guarded by a small number of corporations prevents collaborative learning and improved discovery processes. The sheer volume of available data is prohibitive to thorough exploration and cataloging, potentially hiding value in plain sight simply due to inadequate exploratory resources.

As the second phase of the value chain, **clinical development** comprises everything from preclinical evaluation to phase III clinical trials and includes the submission of an Investigational New Drug application (IND) to the FDA. Supplied with successful targets identified during research and discovery, this phase consists entirely of rigorous, reproducible, and regulated testing. According to Hughes and colleagues, only approximately 1 in 10 compounds that make it to this phase continue to approval and the pharmaceutical market [3]. This is corroborated by the data supplied by TTD, which suggests that approximately 50% of identified compounds make it to clinical development, and only 15% of those are successfully approved [9].

An interesting variation of the typical approval process has been identified due to the COVID-19 pandemic: the Emergency Use Authorization (EUA). Used to help hasten the clinical trial process while also making potentially lifesaving medications available to the public before full approval is granted, EUAs were granted to three COVID-19 vaccinations and one COVID-19 treatment [10]. Currently, EUAs represent a rare mechanism to accelerate the time associated with this phase.

Pain points and problems in the clinical development phase echo several of those from research and discovery, but on a different scale. Whereas research dollars were spread out to maximize the number of discoverable compounds, clinical development dollars are focused on a comparatively small number of projects. This concentration of funding is further exacerbated by the time spent on each project. With a proclaimed need to "fail faster" so that resources can be reallocated to other projects, time is a critical factor in this phase. Clinical trial issues also abound here, including those with data sharing, data integrity, informed consent, recruitment, and retention.

The next phase in the pharmaceutical value chain is **manufacturing and supply chain**. As this phase is the first that is truly visible and has the most immediate impact on the general population, it is also the most noticeably impacted by supply chain disruptions, like those caused by the COVID-19 global pandemic. It is also the most publicly scrutinized, particularly with respect to drugs already on the market. Other recent issues tied to this phase include counterfeit drugs (despite extensive regulation); the presence of carcinogenic contaminants in products manufactured in international facilities; and an abundance of drug shortages attributable to a variety of causes,

including global climate events, shortages of raw materials, political instability, and others.

On a less visible front, this is also the phase that includes the lobbying, discussion, monitoring, and the filing mechanisms of getting a drug approved, including submitting a New Drug Application (NDA). Inspection of manufacturing facilities and processes, official materials associated with the drug, any treatment/benefit claims, and the accuracy and validity of the clinical trials are evaluated here to ultimately determine if the drug will be brought to market [11].

Manufacturing and supply chain pain points are different from the previous two phases and generally fall into two categories: logistics and bureaucratic regulatory processes. Logistics encompasses standard supply chain woes and the necessary communication to properly execute the final stages of the drug approval process. Regulatory pain points include outdated, cumbersome, and even analog processes necessary to pursue approval, as well as the lack of organization and access to data from previously approved medications to make more educated decisions on newer treatments [12].

The penultimate phase of the pharmaceutical value chain is **launch and commercial considerations**. It begins with considerations regarding the release of the newly approved pharmaceutical agent to the public, including the prevalence of the target disease or condition, unique storage and preparation requirements, prescribing restrictions, etc. These factors are then extrapolated to marketing, packaging, commercial coverage, and consumer uptake, ultimately dispatching tightly coordinated efforts to begin recouping much of the funding spent to arrive at this point. At the very least, there are three layers of effort to this phase: one for consumers, one for providers, and one for payors, each with its own intricacies and regulatory framework.

The launch and commercial considerations phase brings an interesting turn to previous problems and pain points. While logistical issues still play a role in distributing the new drug product, revenue becomes the primary focus. Maximizing the efficient use of communication and distribution channels is vital to success. Trust, drug properties, and perceived utility are just a few examples of barriers that must be considered and thoroughly addressed in the efforts tied to this phase.

Lastly, once a new drug product has made it to market, the **monitoring and health records phase** commences. Commonly referred to as phase IV or post-marketing studies, this is the phase where continued surveillance of the drug, its performance, and any associated information is collected, scrutinized, and published, as needed [11]. However, just because a drug product has made it this far does not ensure success. Like others before it, this phase also carries the potential for failure. Several notable examples of drugs that have made it to this phase only to ultimately be withdrawn from the market due to safety concerns include Vioxx (rofecoxib), an anti-inflammatory medication, and Meridia (sibutramine) and Belviq (lorcaserin), two weight-loss medications.

Pain points in this final phase are largely related to accessing and recording reliable data. In a perfect world, these issues would have surfaced during the clinical development phase; however, due to the numerical and characteristic limitations on

the populations studied during that phase, it is common for issues to be dismissed due to statistical insignificance or being overlooked in the targeted population. Adverse effects, special populations, misuse and abuse, quality issues, and even safety issues must then come through specific channels to be properly recorded and explored. The lack of access to and acceptance of many sources of real-world data (RWD) and real-world evidence (RWE), including social media, wearables, and electronic health records (EHRs), limit manufacturers' ability to quickly identify and understand the scope and severity of some issues [12]. Conversely, the same deficiencies can also hinder the recognition of unintended or unstudied benefits of a drug, delaying the steps necessary to offer expanded access and indications.

Increasingly, both technology giants (e.g., Amazon, Apple, Google, Microsoft) and digital health startups (e.g., BurstIQ, EncrypGen, Equideum Health, Patientory) are attempting to capitalize on their resources and expertise in areas including data analytics, predictive modeling, decentralized artificial intelligence (AI) and blockchain to innovate, improve efficiencies, and address pain points in life sciences and pharmaceutical value chain (Fig. 1) [8].

Blockchain and distributed ledger technologies (DLT) are being explored and employed across all five components of the pharmaceutical value chain. Specifically, technology-accelerated approaches for research and discovery include harnessing the potential of data mining, predictive modeling, and AI to identify and prioritize "druggable" targets and candidate medications [13], as well as for drug repositioning—also referred to as repurposing or reprofiling [14]. Clinical development-related targets include digital twins [15] and enhancing clinical trial management and remote participant monitoring [16]. Innovations such as 3D printing medications in drug manufacturing [17] and drug supply chain optimization [18] range from early to late-stage efforts. Combatting challenges with clinical decision support (e.g., alert fatigue) [19], ePrescribing [20], virtual tools [21], and enabling personalized medicine [22] are notable areas within launch and commercial. For monitoring and health records, decentralized medication management systems [23], identity and remote care [24], prescription delivery [25], and adherence [26] are among the efforts to date.

To reiterate, the pharmaceutical value chain has an underlying cyclic nature—one or more steps may be revisited at any time during a drug's life cycle to maintain viability. Manufacturing processes may need to be changed or relocated; off-label

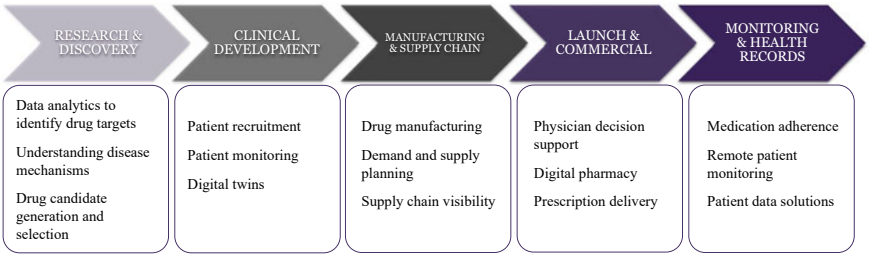

Fig. 1 Technology-focused solutions for the pharmaceutical value chain (Adapted from [8])

use may identify a new indication worth studying, or the brand name and marketing materials may need to be changed due to consumer confusion or common misuse. However, regardless of the circuitous path that may define a specific use case, the pharmaceutical value chain carries high costs, inefficiencies, gaps, and opportunities for technology to improve the process.

2.2 Differentiating Pharmaceutical Value Chain from Pharmaceutical Supply Chain

Before proceeding, the distinction between the pharmaceutical value chain, pharmaceutical supply chain, and medicine value chain is worth noting. The pharmaceutical supply chain, often incorrectly referred to as the pharmaceutical value chain, consists of all elements of the manufacture and distribution of pharmaceutical products. It is most succinctly represented in the third phase of the pharmaceutical value chain, aptly named manufacturing and supply chain, and is considered by most to include the regulatory requirements that accompany the physical manufacture and movement of pharmaceuticals.

Conversely, the medicine value chain deals with the specific monetary pricing and associated 'real' value of medicines. Comparatively, it represents a truncated or alternately aligned version of the full chain. Outlined by Aitken in "Understanding the pharmaceutical value chain," this oft-cited but narrow interpretation of the full value chain combines the research and development phases with the manufacturing and supply chain [27]. Because Aitken's article focuses on easily traceable costs, the less directly attributed costs of research, discovery, and development are obscured through this reorganization. While simplifying the cost structure is sufficient for his needs, it diminishes the ability to effectively see and address each phase and its pain points. To fulfill the purpose of demonstrating the potential value of blockchain across the entirety of the life cycle of a pharmaceutical product, this narrowed view is therefore discounted in favor of the more comprehensive alternative.

3 Blockchain Efforts Within Pharmaceutical Industry

Despite the relative novelty of blockchain and DLT, numerous efforts are already underway to identify and explore the benefits they may offer to the pharmaceutical industry. Consider the following use cases. The pain points that they specifically address will be further discussed in a later section.

3.1 Pharmaceutical Users Software Exchange (PhUSE) Blockchain Project

The Pharmaceutical Users Software Exchange (PhUSE) was founded in 2004 in the United Kingdom as a community where pharmaceutical programmers could discuss ideas and shepherd the industry's future direction [28]. Now a global, independent, and volunteer-run non-profit organization, PhUSE has taken on issues like data transparency, open-source technology, data standards optimization, and frequently assessed emerging trends and technologies, not the least of which is blockchain [28].

In 2017, their efforts began with the question of how blockchain can offer solutions across the entirety of the pharmaceutical value chain; in 2018, PhUSE published its first report on the transformative promise offered by blockchain to both the pharmaceutical and healthcare industries. After identifying blockchain models that could be useful in healthcare, the report gave several examples of how blockchain could improve existing pain points. Two use-case projects were outlined that had the potential to quickly illustrate and capture the benefits of blockchain while simultaneously serving to lay the necessary groundwork for the multitude of changes that must be undertaken to fully embrace the technology. The two projects recommended were: the use of smart contracts to maintain efficiency and quality in the supply chain (modeled from other industry uses and adapted) and increased access to and transparency for patient data through a blockchain-facilitated patient portal-type function [29].

In 2020, PhUSE published Phase 2 of the project, focusing on blockchain applications in the pharmaceutical industry, explicitly emphasizing the improvements it could bring to the clinical trial process. They set about to deliver a proof-of-concept solution that addressed the following four needs: patient identification, data infrastructure, eConsent tools, and architecture specialists [30]. Using Ethereum, they were successfully able to build proof-of-concept, however, they highlighted the inefficiency of the platform for real-time data sharing needs, stopped short of calculating the return on investment, and noted complications with integration and the various user interfaces. Still, the successful deployment of both patient identification and consent/enrollment tools, as well as the validated model for protected, shareable data, are vital steps in developing industry interest and trust in the application of blockchain.

3.2 Innovative Medicines Initiative (IMI) Blockchain-Enabled Healthcare

The Innovative Medicines Initiative (IMI) is a byproduct of the European Technology Platform on Innovative Medicines (aka INNOMED) [31]. Established in 2007, the first IMI Initiative (IMI1), executed as a public–private partnership (PPP) between the European community and the European Federation of Pharmaceutical

Industries and Associations (EFPIA), was created to improve the drug development process and ultimately create safer and more effective medicines [32]. After 7 years of prolific, breakthrough research and documented progress on the project initiatives, IMI2 was created in 2014 to continue the undisputed success of IMI1 and build on the advancement and momentum it generated [31].

One of the more ambitious projects of IMI2 was "Blockchain-Enabled Healthcare." Designed to include and represent stakeholders from the entirety of the healthcare system, the blockchain-enabled healthcare program built upon the associated momentum of PhUSE and endeavored to establish an incentive-based blockchain ecosystem that could be used unilaterally by the pharmaceutical industry for development, manufacturing, and distribution needs [33]. One of the notable outputs of this industry group was their conceptual approach to a blockchain-enabled healthcare system, which they delineated across a three-layer proposal (Fig. 2).

Understanding the difficulty in maintaining oversight of a distributed service, IMI2 also established a Healthcare Foundation feature as both a governance and integration structure [33]. Their primary development was PharmaLedger, a blockchain-enabled consortium currently comprised of 29 members, including ten European Union Member States, Switzerland, Israel, and the U.S., along with representatives from the EFPIA, subject matter experts, research centers, hospitals, patient organizations, etc. [34].

PharmaLedger is focused on leveraging blockchain for the supply chain (e.g., anti-counterfeiting, clinical product traceability, e-leaflet, finished goods traceability), clinical trials (e.g., recruitment, e-consent), and health data (e.g., connected health devices, networked Internet of Things (IoT) medical devices, remote patient monitoring). Complimentary efforts include the combination of blockchain, machine

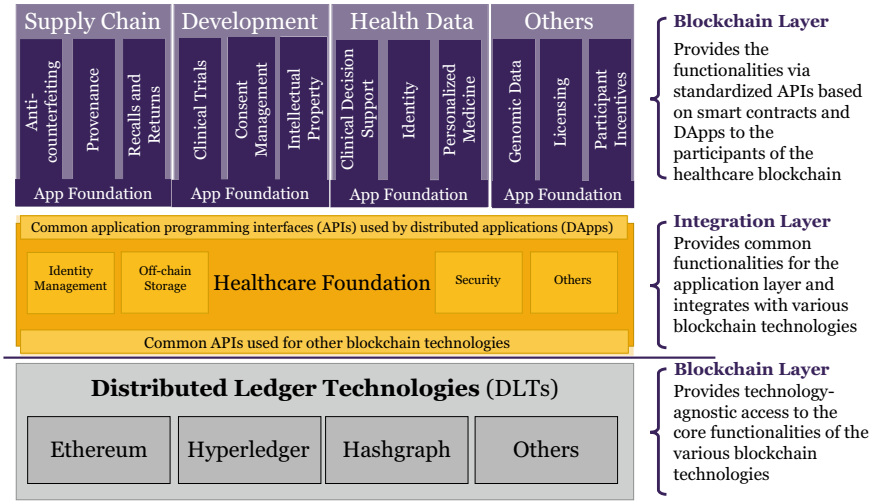

Fig. 2 Layered proposal for a blockchain-enabled healthcare system (Adapted from [33])

learning (ML), and AI to help realize value-based healthcare delivery via personalized medicine. The project is ongoing as its roadmap outlines a three-stage approach of design and foundations, followed by development and deployment, culminating in validation and sustainability. PharmaLedger has also committed to privacy and transparency in health data, a secure and trustworthy supply chain, improved patient ownership of health data, and accelerated clinical development through innovation in the clinical trial process.

3.3 The MELLODDY Project and Millions of Molecules Blockchain + Smart Contracts for Human Participant Regulations and Consent Management

The MELLODDY project (Machine Learning Ledger Orchestration for Drug Discovery) is another endeavor from IMI2. A blockchain-based, federated ML platform, MELLODDY is designed to leverage proprietary data without compromising it; the aim is that the program will be able to glean insights from the independent drug discovery efforts of multiple private entities without disclosing the source [35]. A unique component of this model is that the analysis includes not only data points from millions of biochemically-active small molecules but also several hundred terabytes of image data—the insights from which companies could use both retroactively and with future discoveries to help accelerate and improve drug development [36].

3.4 Information Exchange and Data Transformation (INFORMED) Initiative

Whereas PhUSE is a predominantly private-backed initiative, and IMI2 is a PPP, the Information Exchange and Data Transformation (INFORMED) Initiative is a modified PPP endeavor operated by the FDA and comprised of government, academic, non-profit, and industry members [12]. INFORMED was started in 2016 by the Office of Hematology and Oncology Products to improve data aggregation, organization, and mining for oncology products. While oncology was the initial driver of the program, the draw of similar open access data-sharing technology provided through blockchain expanded the project to include ways to leverage all existing data, including images, test results, RWD, RWE, and other digital or digitized sources [37].

3.5 Moneyball Medicine

'Moneyball medicine' is a phrase that entered the lexicon in 2012 [38]. Drawing on the lessons in Michael Lewis' 2003 book, Moneyball: The Art of Winning an Unfair Game, the authors posit that the moneyball concepts of evidence-based decision-making and associated value determination apply to baseball and medicine. Based on this association, they offer the accountable care model of healthcare as the true test of moneyball medicine, with the added caution that all cost-effectiveness models are only as solid as the data and the assumptions on which they are built.

Fast-forward five years to the publication of the book MoneyBall Medicine, a commentary expanding previous points but with a more specific perspective: data and analytics are the true drivers of evidence and transformative value in healthcare [39]. Unfortunately, the ubiquity and volume of data now involved in daily healthcare operations and accumulated over the last decade demand better data-oriented tools and improved models. Glorikian specifically notes the importance of AI and ML tools for drug discovery and repositioning, emphasizing the importance of deploying advanced data-driven technology to provide increased value at a reduced cost [40]. While he did not specifically mention the use of blockchain, his forward thinking identifies with one of the many identified use cases for applying blockchain in data analysis and management.

In summary, both the realized and unrealized value of blockchain in healthcare are becoming evident. With pioneering efforts coming from both the public and private sectors, sometimes in unique collaborative partnerships, healthcare's costly and inefficient pain points are being reimagined and resolved through the innovative avenues offered by DLT.

4 Mapping Blockchain Characteristics to Pain Points in the Pharmaceutical Value Chain

4.1 Adapted Fit-For-Purpose Framework and Design Elements

As many of the projects in the previous section can attest, blockchain and the characteristics of DLT are well-suited or easily adapted to specifically address known pain points in the pharmaceutical value chain. This can, at first, be confusing; the known problems and pain points from each of the five phases of the chain are varied and intrinsically different. Clearly, one solution cannot solve them all. However, the flexibility and adaptability of the DLT fit-for-purpose framework [16] allows for the manipulation of individual design elements to arrive at a perfect-fit solution.

Looking back to the PhUSE example, the well-known and established frameworks, Ethereum and Hyperledger Fabric, were compared for appropriateness-of-fit

for prospective projects. While neither framework was ideal for all the intended use cases, different design elements of each were selected to create a best-fit-for-purpose framework. Borrowing the smart contracts, tokenization/incentivization, and benchmarked automation of Ethereum, and the private permissioned setup of Hyperledger Fabric, a health system could set up an incentivized blockchain security network protecting access to internal data, ensuring only approved parties can access the private data within and keeping out malicious entities like ransomware [29].

This example also highlights the importance of feature tradeoffs. Different features and design elements impact the end functionality of the framework. Therefore, it is important to analyze which blockchain elements are essential for a project, allowing others to be modified or displaced in favor of functionality. This will be addressed further in the following subsection.

4.2 Matching Characteristics (e.g., Decentralized, Distributed, Conditionally Immutable, Scalable, Cryptographically Secured) to Identified Pain Points in Each of the 5 Categories

Looking back to the pain points and problems identified in the pharmaceutical value chain, there are many opportunities for technological intervention and improvement, specifically through features of DLT.

Starting with the research and discovery phase, pain points have been identified in dealing with the sheer volume of available data, limited financial and exploratory resources, data siloing to protect proprietary interests, and inhibited research progress due to the resulting data separation. In short, a faster, less expensive method is needed to examine proprietary data distributed among many sources without compromising ownership. A quick glance back at projects already underway indicates that a solution is already being tested for this: MELLODDY. Applying the decentralized, distributed, security, traceability, authentication, practical immutability, and scalability attributes of blockchain to a federated ML model, MELLODDY accomplishes the following [35]:

- Improved speed of analysis at a reduced cost
- Access to protected IP without compromising it
- Collaborative learning without data or learning centralization
- Instant applicability of insights to proprietary data
- Decreased lead generation time.

The next chain phase, clinical development, is probably one of the more heavily researched areas of applicability for blockchain elements. It is also one where tradeoffs will need to be considered based on project priorities. Common complaints during clinical trials include lack of data sharing capabilities, both real-time and delayed, possible data duplication due to inter-site blinding, recruitment, retention,

duration, and the inability to efficiently analyze data for meaningful observations. Summarily, all of these issues also result in high costs.

Several examples have already been presented both in previous sections and the literature to address these issues. Starting with consent and enrollment, PhUSE recommended using a tokenized voiceprint recorded on blockchain to establish unique identities. The decentralized nature of blockchain, consensus authority, incentivization, and near-immutability of the data not only made it hack-resistant but also allowed patients to provide access to their information across multiple different organizations with minimal effort [29]. They then used this system with the addition of smart contracts and automated benchmarking to manage informed consent documentation, ensuring the correct form was signed and accessible to the right site at the right time and that necessary procedural cascades were consistently performed per protocol. Similarly, models leveraging blockchain for improved research participant recruitment, retention, and research data sharing have been proposed [41].

Approaching the problem from a different perspective, PharmaLedger embraces the view that token incentives can be used to anchor large volumes of information to the blockchain without actually being incorporated into the blocks. This key difference maintains the security and tamper resistance of the anchored information through standard blockchain principles but affords the user control over their information by requiring the token key for access. In this example, a universal health identifier and record would be stored for each patient, decentralized across the network. Any time the patient's record needed to be accessed, the owner's key can be provided via an encrypted interface, allowing access only for as long as needed. The previous data cannot be compromised. Any new data entered in the record are anchored in new blockchains linked to the same patient identifier and EHR. Because real-time access is desired across this system, block size is minimized, and transaction speed is maximized by anchoring information to the chain instead of directly incorporating it. This essentially allows the network to act as a high-level health information exchange with no interoperability issues because blockchain contract rules set the standards for data.

In these cases, as well as many others, recruitment, retention, monitoring, protocol compliance, data management, data analysis, and data transparency are aided by the decentralized and secure nature of blockchain while consensus mechanisms (e.g., proof-of-stake (PoS), proof-of-authority (PoA)), tamper resistance, and the distributed nature of blockchain protect data from corruption, integrity, and privacy concerns [42]. Additionally, the use of smart contracts can appropriately display identifiable or de-identified data depending on the user access permissions, maintaining blinding, aiding in faster recruitment of eligible patients, and ensuring proper follow-up with primary care teams regarding participation and monitoring.

The pharmaceutical value chain's manufacturing and supply chain phase is already benefitting from advancements in other industries that deal with logistics in both manufacturing and distribution. While regulatory processes have been implemented to improve track and trace functions, blockchain's near-immutability, consensus mechanisms, transparency, and distributed nature make it unparalleled for use in this sector. Counterfeit medications, unapproved source products, chain-of-custody

traceability, audit trails, and even false claims are all addressed with blockchain elements [43]. Because counterfeit and unapproved products and source materials lack the transparent and traceable audit trails that establish provenance and chain-of-custody, it is easy to ferret them out or avoid them entirely. False claims are also easily spotted, as corresponding invoice audit trails easily corroborate or refute possession of the allegedly dispensed product. Plus, blockchain can easily be traced and verified through a marker as simple as a QR code or similar encoded tracker for in-network entities [44].

The predominant benefits of blockchain on the launch and commercial considerations phase of the chain are improved ease of dissemination and transparency of data and reduced cost recovery. As previously discussed, commercial efforts related to drug launches revolve heavily around positioning, pricing, and maximizing revenue recoupment from the previous phases of the chain. The reduced costs from all previous phases contribute directly to reduced revenue needs here, resulting in potentially industry-altering methods and rates for pricing newly released drugs. Payment and reimbursement models governed by smart contracts would speed up payments and approvals by decentralizing an unnecessarily slow, centralized process [45]. Additionally, the security, scalability, and transparency of blockchain allow for rapid and more cost-effective dissemination of drug-related information, improving regulatory-based efforts as well as marketing and medical knowledge.

Finally, blockchain features can be immensely helpful in post-launch monitoring and health records. Aligned with the aforementioned improvements in clinical trial enrollment and tracking, blockchain-based programs could have faster and more comprehensive access to patient-reported issues and events; all kept secure, private, and immutable through the core principles of blockchain. In the same line, blockchain-based record and data management would make it easier to trace and notify affected parties of problems or concerns that arise with a drug. In the event of a drug recall, blockchain-based tracking systems would facilitate rapid and complete notification and collection or disposal of recalled lots.

5 Blockchain—But Not in a Vacuum

5.1 Blockchain-Complementary Established and Emerging (e.g., Machine Learning, Artificial Intelligence) Technologies for the Pharmaceutical Value Chain

Blockchain offers a great deal of transformative promise to healthcare and the pharmaceutical industry. However, as the projects highlighted in previous sections have shown, it is not a standalone, one-size-fits-all solution. Rather, it is a tool among many that can be collectively leveraged to improve known problems and issues facing healthcare. The MELLODDY project combines blockchain with federated ML and AI to efficiently and securely deliver on its promise. Without applying the

ML model and the AI capable of using it, even blockchain could not effectively overcome the issues that accompany overwhelming volumes of siloed proprietary data. Similarly, PhUSE acknowledged that a major component of any blockchain-based technology needed to include a team of architecture experts, ensuring that the data shared, captured, and analyzed on the network was available and usable to the parties who need it [30]. Having information on the blockchain is useless without the applications and interfaces necessary to read and interact with it. Members of the Decentralized Trials and Research Alliance [46] have also launched efforts leveraging blockchain-complementary technologies and approaches, including the use of privacy-preserving, federated ML with the Veterans Incentivized Coordination and Integration initiative as a Data Integrity and Learning Network focused on veteran well-being [47]. Arguably, the most positively radical approach in the quest for "faster medical miracles" is Distributed Autonomous Science, which would theoretically require either a complex distributed autonomous organization (DAO) or a "complex series of more simplistic DAOs" to achieve those goals [48].

Consider a project with multiple stakeholders who all need access to the same set of information but with different access permissions, like a clinical trial. Middleware, interfaces, application programming interfaces (APIs), and associated infrastructure must be developed to recognize different stakeholder roles, request appropriate tokens/keys, and display only relevant or approved information. Patients should not have access to global study data, just as researchers should not have access to blinded study information, and data analysts should not have the ability to add new data. Blockchain frameworks can secure, transmit, approve, store, track, and audit data. However, even smart contracts are limited in how they can be applied, as any rules built into them apply unilaterally to every node and data point on the network.

Blockchain is also being used in telehealth and virtual reality spaces (Equideum) [47]. Outfitted with AI programming, it is helping rehabilitate patients dealing with addiction, psychosocial, and other mental health issues, as well as pain management, communication, and even incarceration [49]. Other applications include natural language analysis and processing, neural networks, evidence-based non-pharmacological, clinical intervention, and behavior modification models.

Ultimately, the important element is this: solutionism must be avoided. Blockchain alone is just a tool, not a solution. As in many other circumstances, it is important to match the best solution to fit the need. Combining blockchain with other established and emerging technologies is essential to successful implementation and solutions.

6 Debunking Myths Around Challenges with Blockchain

6.1 The Myth of the Technical Challenge

There are undoubtedly barriers to fully realizing the potential benefits of blockchain utilization in the pharmaceutical industry. However, the most resounding and easily

debunked is that the technology is the primary roadblock and is too challenging to implement.

This myth is perpetuated on three fronts: user interaction, infrastructure, and integration.

As demonstrated by both PhUSE and PharmaLedger, it is possible to leverage other technologies, including middleware, APIs, and custom user interfaces, as well as interprofessional communication, to effectively create solutions that deliver a user-friendly experience. In fact, PharmaLedger is built on the premise that the technology can be seamlessly and artfully applied to increase consumer confidence in technology generally beyond the scope of comprehension of the general public [34].

This myth also likely originates in the generally accepted knowledge that customization is associated with confusion and cost [50]. As one of the most useful attributes of blockchain is its flexibility and adaptability to any set of circumstances or problem, customizability is essentially another core feature of the technology. Nevertheless, because the most well-known and discussed use cases for blockchain happen to be cryptocurrencies, their frameworks can be perceived as immutable as the data they contain, further stressing reconciliation with the idea of adaptable architecture. Similarly, across almost any industry, healthcare notwithstanding, customization leads to increased costs. Based on the assumption that there is a 'base model,' customization or personalization is equated with 'upgrading.' Specifically in the world of technology, improving transaction speed, scalability, traceability, data management, and data analysis all generally equate to higher cost and greater resource utilization in previously established models.

So, it comes as little surprise then that the guise of technological challenges is superimposed over other outdated and inapplicable standards from the very historical programs and procedures that blockchain helps overcome.

Fortunately, this myth is fairly easily dispelled, not only through the diligent preliminary work done by multiple pioneering entities but also through the understanding that the very basis of blockchain is founded on the concepts of trust, traceability, and security modified to meet the needs of its users.

6.2 The Reality of Challenges Tied to Change Management, Resource Allocation, Paradigm Shift, and Reaching Consensus

Instead of reflecting true technology challenges in the use of blockchain, the technology myth is more likely founded on the fearful understanding that underlying and disparately managed systems will need to agree upon and conform to specific standards to maximize benefits.

Technological and procedural entrenchment is often a hallmark of large organizations and institutions, so much so that an entire field of study has been dedicated to change management or the successful transition from one system to another.

User buy-in, training, education, planning, commitment, and follow-through are all necessary for successful change management. The culture within the organization is also a necessary element to identify and navigate. Properly implemented, change management can go very smoothly; but poorly attempted or implemented change management can not only result in failure and further entrench the organization in outdated practices and ideals. Perhaps one of the most recent areas where this has played out is the implementation of EHRs. Multi-million dollar projects that took years and countless resources to execute revolutionized the practice of evidence-based medicine across the world. The improved efficiency, availability of and access to data, and clarity and organization of information were a stark contrast to the slow, disorganized, and cumbersome practice of paper charting.

So, it is with blockchain; planning, resource allocation and management, consensus understanding of underlying needs related to both input and output, and a desire for change will all be necessary to face the fear and defeat the myth.

Fortunately, recognizing the inherent challenge in realizing this paradigm shift, forward-thinking organizations and individuals have built partnerships and collaborative efforts to identify and address these needs. Through their continued efforts, the world is gaining an understanding of how adaptable and controllable blockchain implementations are, the realized benefits of blockchain utilization, and the next challenges to tackle to improve its application.

7 Blockchain and The Idea Pipeline

New use cases for blockchain in healthcare and pharmaceuticals are constantly being discovered and explored. Some are building off the success of established uses, while others are forging new pathways that take advantage of blockchain's unique features. The following are examples of areas where blockchain is being explored or could prove beneficial.

7.1 Pharmacogenomics

Blockchain applications are already being successfully combined with other technologies and applied to massive data stores to efficiently and thoroughly analyze existing data, particularly in new drug discovery. However, much remains to be discovered about the underlying mechanisms of existing medications and known compounds, including comprehensive biological action, interactions, and alterations based on genetic factors. With improved computing power, distributed networks, privacy assurances, and the appropriate application of ML algorithms and AI, blockchain could usher in a new era in personalized medicine through an immense expansion of the understanding of the interplay between pharmaceutically active compounds and variations in the human genome and genetic expression. Early efforts

for this include the use of Ethereum for storage and querying of pharmacogenomic data via smart contract capabilities [22], as well as commercial interests seeking to address core pain points of sequencing costs, regulatory costs, and privacy [51].

7.2 Collaborative Pharmaceutical Development

One of the stated goals of several initiatives, including MELLODDY, is to improve the analysis of existing compound knowledge, facilitate identification of existing molecules for pharmaceutical development, and enhance discovery of new molecules. However, in doing so, MELLODDY aims to preserve the origin of information to protect IP rights. While this is not inherently problematic, it does eliminate the possibility of uniting researchers on parallel but unequal research paths.

In the present market, many new molecules and products are being discovered or created by small companies lacking the resources for large-scale study and development. To remedy this, many seek to partner with large-scale pharmaceutical manufacturers to hasten the journey down the pharmaceutical value chain and hopefully create a mutually beneficial partnership. However, this model still relies on one company conducting the preliminary research and a second company leveraging their experience and resources to improve the process.

Meanwhile, it is not uncommon for different pharmaceutical companies to expend resources in research and development only to abandon a project similar to, but behind that, of a promising competitor. Realistically, the resources of all parties involved could have been optimized if the concurrent research was complementary instead of parallel. The combined efforts of both teams could have arrived at any number of conclusions faster and through reduced resource expenditure had they been working together.

To that end, the question must be asked if there is a way for a blockchain-based program to encourage collaboration between entities doing similar but unequal research? This approach could develop similarly to the 'coopetition' model [52, 53] that blockchain enabled with the [54] via the use of Quorum (i.e., enterprise, permissioned version of Ethereum). Coopetition allowed companies with traditional competing interests in the healthcare provider data management space (i.e., Aetna, Humana, MultiPlan, Quest Diagnostics, UnitedHealthcare) to form a consortium and work together for the mutual benefit of all participants [55]. The use of smart contracts to negotiate agreements between parties could also be used to create a standardized path for collaborative research, further accelerating clinical development. Regardless of the outcome, it would improve and decrease resource utilization while reducing the time needed for a fully developed discovery.

7.3 Patient Access, Medication Reclamation, and Prescription Waste Reduction

The cost of individual cancer drugs and biological agents commonly have prices surpassing $10,000 each per month [56], which functionally limits patient access to these lifesaving agents. Perhaps counterintuitively, prescription waste has also been observed to occur in up to 41% of patients receiving oral cancer drugs—chiefly due to cancer progression, death, and toxicity [57]. This disconnect highlights that financially driven health disparities in vulnerable patient populations are concurrent with an avoidable waste of sealed, single-dose packaged oral oncolytics.

One novel application of blockchain technology in the pipeline aims to address challenges around patient access and financial toxicity associated with high-cost cancer medications. Their approach to medication reclamation and redistribution also may provide ancillary benefits, including reducing prescription waste and environmental pollutants, as well as yielding valuable supply chain data and related indicators for this category of surplus medication. On the front end, RemediChain [58] encourages and incentivizes citizens to text #FlipYourScrip to donate unopened, unexpired medications along with a picture of the medication packaging. Upon receipt of the picture and information, RemediChain will either: (1) direct individuals to a safe drug disposal facility if the medication is not suitable for redistribution—including providing a gift card for those who opt to text a picture from the drug disposal unit, or (2) provide free shipping via a partnership with FedEx if the medication can be donated to a patient in need. After launching this campaign, in 2021, RemediChain was able to match high-cost cancer medications with nearly 100 patients who otherwise would have gone without these lifesaving treatments (Fig. 3).

On the back end, the RemediChain platform is leveraging blockchain technology to create a surplus medication database with shared governance via forming an international consortium of research universities, cancer centers, and other stakeholders.

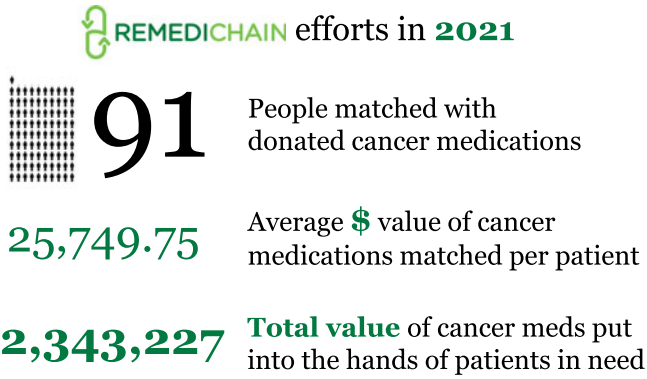

Fig. 3 Number of patients matched with high-cost cancer medications and value in US dollars of matched medications by RemediChain, 2021 [58]

This platform also helps fill a related need, as no single organization is responsible for oversight of prescription waste, nor is tasked with tracking the precursor of prescription waste—surplus medications; consequently, the net impact of prescription waste (e.g., financial, health, and environmental) is unknown. Surplus medication research enabled by this platform could have implications in pharmaceutical sciences, population health, and environmental sciences. While RemediChain primarily focuses on the US pharmaceutical industry, its research could also be localized for low- and middle-income countries. Importantly, while concurrently putting medications into the hands of patients who need them, this research into surplus medication can lead to innovative processes, methods, and systems that prevent the conversion of surplus medication to prescription waste and increase the conversion of surplus medication into reclaimed medication for distribution across low-resource settings at scale.

7.4 The Evolution of the Traditional Retail Pharmacy

The traditional pharmacy dispensing model is under immense strain to maintain the line between safety and profitability; specifically, retail pharmacies find it increasingly difficult to do both. While unpopular, the idea of repositioning pharmacists in a dispensing model is essential to restoring profitability and improving patient safety and service.

Blockchain has already been shown to streamline the pharmaceutical supply chain and payment systems through smart contracts, traceability, and the use of micropayments [45]. While pharmacists are necessary to assess the safety and appropriateness of highly variable prescription orders, their participation in product preparation is a misuse of resources in a system where blockchain can be implemented. Freeing pharmacists from these tasks enables them to engage in cognitive- and service-based efforts (e.g., patient counseling, education, immunization, therapy reviews). This, in turn, fundamentally alters the systemic perception of pharmacist value, allowing value-based models to reimburse them for targeted health outcomes and care provided, as opposed to product dispensed.

While regulatory challenges make this opportunity challenging to capitalize on, it should be noted that an opportunity does, in fact, exist. Reimagining the pharmacist's role to exclude supply-chain activities that can easily be automated, tracked, and audited safely, an end-to-end value-based model could be put into play, improving patient safety, patient satisfaction, and pharmacists' capacity to apply their skills and knowledge where it is most needed.

These are only a few areas where blockchain could profoundly impact the pharmaceutical industry in the near future, based on existing utilization and anticipated opportunities. However, only the surface has likely been scratched concerning the positive and transformative impact blockchain can have on the future of pharmaceuticals.

8 Future Directions

The World Economic Forum highlighted that COVID-19 has emphasized the need for a cross-sector approach to collaboration in healthcare, necessitating new models (e.g., coopetition) and approaches [59]. The timing may also be right for the innovation-minded, as 76% of business executives recently indicated the need for new ways of collaborating (i.e., data sharing) with ecosystem partners and other stakeholders. Those sentiments align with findings from Gartner that collaborative data use via decentralized approaches is a major strategic trend across industries going forward [60]. This functional groundswell of support for both the philosophical underpinnings of blockchain and what it enables from a pragmatic perspective suggests a heretofore unseen openness to change from the most disruption-resistant sector on the planet—healthcare.

This same theme of change has been realized in pharmaceutical research and across each component of the pharmaceutical value chain, potentially buoyed by applying emerging concepts like the Internet of Behaviors [60]. Just as the IoB has been suggested as a means to harness wearable technology and "digital dust" to influence decision-making in other sectors, its use of data, incentives, and disincentives could be applied to various stages along the pharmaceutical value chain. The approach itself is not particularly novel, as decades ago, texts like "Persuasive Technology: Using Computers to Change What We Think and Do" [61] illustrated this type of potential. However, the ubiquity of data, development of DLT-supported smart contracts, opportunities for privacy-preservation (e.g., zero-knowledge proofs, homomorphic encryption, federated learning) [62], and impetus for change have never been more pronounced than now. What remains to be seen is how tools for innovative change like this might be optimally employed while recognizing the critical need to address the accompanying ethical and societal challenges.

9 Conclusions

The pharmaceutical value chain encompasses much more than the subset of the pharmaceutical supply chain, which is limited to the elements of manufacturing and distribution. The five phases comprising the full pharmaceutical value chain: research and discovery; clinical development; manufacturing and supply chain; launch and commercial considerations; and monitoring and health records each suffers from pain points that have collectively resulted in a ponderous 17 years from "new idea to treatment" [48]. Blockchain is a relatively new addition to the arsenal for advancing pharmaceutical research, but when combined with other established and emerging technologies (e.g., AI, ML), has already begun to address these impediments via industry and PPP efforts (e.g., MELLODDY, PharmaLedger). While technology-related obstacles have slowed the adoption of some blockchain-facilitated solutions, challenges with change management and awareness deficits of future-facing models

like coopetition can prove even more problematic to leveraging DLT to address the desired pain points. Those who can successfully shepherd their laboratories, organizations, universities, systems, and consortia to maximize the benefits of DLT while navigating hurdles will be well-positioned to make a positive impact on the lives of patients, industry participants, and global heath.

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