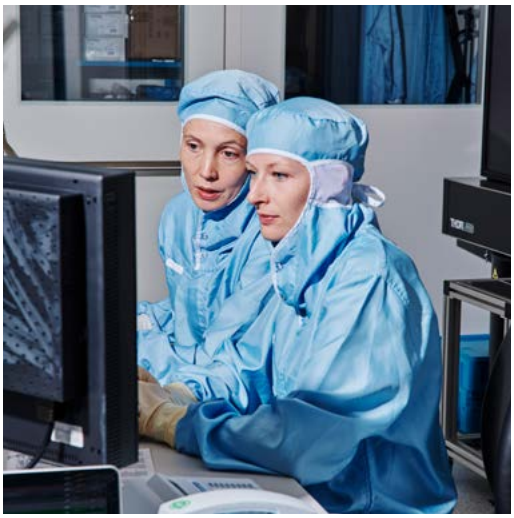
Benefits of blockchain-based supply chain networks for the pharmaceutical industry

A hypothetical pharma company reduces complexity, generates more revenue and grows value for their entire ecosystem.

PharmaNet: A model for an end-to-end chain-of-custody network

Our hypothetical industry network provides end-to-end traceability and condition monitoring, veri iable identity management, advanced inventory management and consent-based patient adherence tracking.



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Supply chain application networks

Multi-enterprise processes require multi-enterprise software solutions

Supply chains don't buy software. Individual enterprises do. It is perhaps for that reason that the vast majority of business software is *enterprise centric*. However, many, if not most, business processes are *inter-enterprise* in nature. The placing of a purchase order by one company triggers the creation of a sales order at the supplier, starting a chain of activities which may include buying raw materials from suppliers, production of the goods by outsourced manufacturers, packaging by a third party, a whole set of logistics activities involving third-party logistics providers (3PLs), carriers, inspectors, insurers, and other third parties, and ultimately payment involving banks and payment service providers.

Multi-enterprise processes require multi-enterprise software systems. And multi-enterprise software is architected very differently from single-enterprise software. We refer to this type of multi-enterprise software as a "supply chain application network"—i.e., a network of companies tied together by shared applications, processes, and data.

Supply chain application networks are built to solve multi-enterprise challenges. A number of these networks have been developed over the past two decades to solve problems such as procure-to-pay, logistics and global trade, multi-tier channel management and collaborative demand management, as well as industry-specific xchanges. Some of them have hundreds of billions or even trillions of dollars of transactions flowing through their network. These networks enable the creation of multi-party digital supply chains with automated processes. They form the foundation for autonomous supply chains, where more and more of the routine processes can be performed without human intervention.

What is a supply chain application network?

Different from single-enterprise apps (e.g., ERP, CRM, etc.), a supply chain application network is a platform connecting a network of trading partners. It is also different from messaging networks, which generally employ EDI and XML messaging between participants. A supply chain application network has:

- Multi-enterprise applications, executing on the networked platform
- Multi-enterprise process orchestration
- A single version of the truth, i.e., common, shared and persistent transaction¬al and master data, residing on the network platform
- Multi-party security, master data manage¬ment, and process flows

For more, see Supply Chain Networks Revealed.

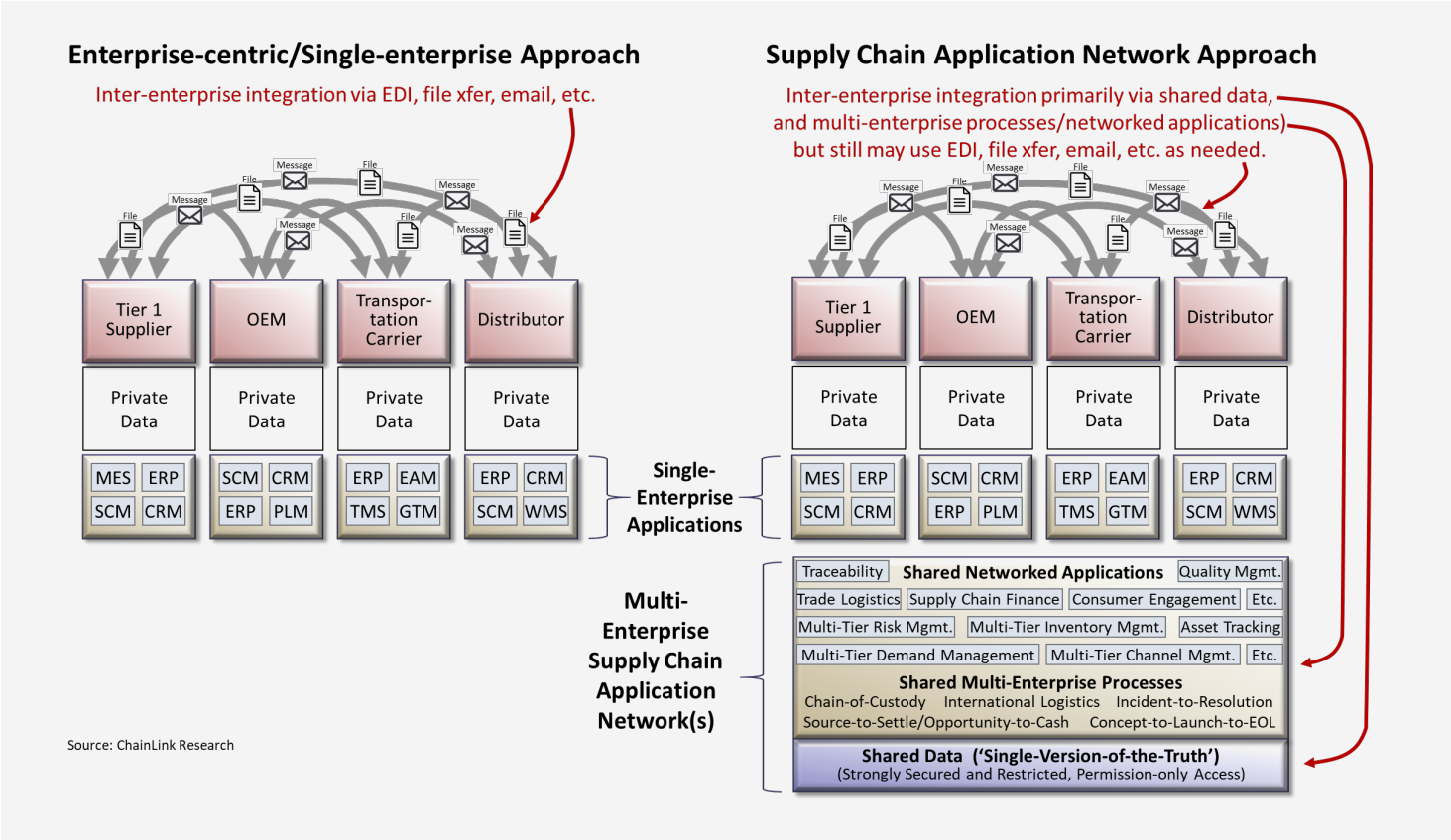

Figure 1 – Enterprise-centric applications vs. the supply chain application network approach

What if the supply chain application network you need does not exist?

Challenges in creating supply chain application networks
What can a business do if the supply chain application network it wants does not yet exist? That is a common scenario, since there are a limited number of networks in existence and a nearly unlimited number of high-value use cases that have not yet been built. Unfortunately, creating a viable supply chain application network from scratch requires a tremendous investment, typically in the ballpark of $100M or more.[1] It usually takes more than a decade to create the technology platform, then build, prove out, and refine obust applications on the platform, hone the business model, and build up a critical mass of participants (see side bar, *"Key elements of a supply chain application network"*).

This would be daunting even for a company that has software competencies but has never built a network like this, and even more daunting for a company that does not have software engineering, productization and marketing as a core competency. The technical challenges alone are significant sin e a network architecture is substantially different from the much more common single-enterprise application architecture. However, the business challenges are often as big as or greater than the technical challenge. Th is includes fi uring out how to incentivize participation to build up a critical mass of trading partners to achieve a network effect while coming up with a business and revenue model that is sustainable and that participants are willing to pay for the value received.

A faster way to create a supply chain application network
Blockchain technology provides a shared database between multiple parties without requiring a centralized third party. Blockchain technology can thereby serve as a foundation for creating a blockchain-based supply chain application network

[1] ChainLink has had in-depth briefings and orkshops with many of the successful supply chain application networks. Most of them invested in the neighborhood of a hundred million dollars in R&D, marketing and participant recruiting, over a period of a decade or more, before they reached a critical mass of capabilities, customers and participants.

(BSN). Blockchain technology by itself does not solve most of the challenges listed above, and some versions can suffer from performance limitations.[2] Fortunately, major technology providers have put together managed blockchain services that help with much of the technical heavy lifting. Examples include IBM Blockchain Platform and IBM Blockchain Services, Amazon Managed Blockchain, Microsoft Azure Blockchain Service, and services from other providers such as Oracle, Google, and others. Of these, in our assessment, IBM provides the most comprehensive set of capabilities and services, especially for solving supply chain challenges (for more details on this, see *Appendix A: IBM's blockchain offering for building a BSN*).

The rich set of services IBM offers allow companies that do not have software engineering as their core competency to create and manage a BSN. IBM uses the terminology "convening a network" rather than "building a network," as they offer a lot of pre-built application-level software, experience, and knowledge, and can do much of the technical heavy lifting. Together, these technologies and services allow someone to convene a BSN in a much shorter time and far below the cost of building one from scratch, without having to recruit extremely scarce and costly blockchain engineers. A minimum viable network can be brought up in commercial production use within a matter of months, and a critical mass of functionality and participants can be reached within as little as two to three years, rather than a decade or more.

Estimating the value of a blockchain-based supply chain application network (BSN)

Hypothetical BSNs illustrate value generated

BSNs can bring immense value to the convener and to the participants along many dimensions. To help illustrate this and better understand the magnitude of value that can be generated, we describe some industry-specific s enarios. In this paper, we focus on a hypothetical BSN that provides chain-of-custody-related application functionality for pharmaceutical supply chains. This proposed network tracks the handoffs and monitors pharmaceutical products' condition at a serialized unit level from the point of manufacturing to the point of consumption by the patient. It includes multi-party applications such as traceability, inventory management, cold chain, anti-counterfeiting, expiration management, regulatory compliance, and patient adherence. The capabilities of this hypothetical pharmaceutical BSN are described in more detail in the section below titled A *"produce-to-use" chain-of-custody solution*.

[2] Public blockchains, such as bitcoin, suffer from limited scalability. The global bitcoin network maxes out at about seven TPS (transactions per second), whereas the major credit card networks claim to handle up to 65,000 TPS—almost 10,000 times more than bitcoin. Some private blockchains use much more efficient consensus algorithms to achieve better scalability.

Key elements of a supply chain application network

- Multi-enterprise platform
  - Canonical multi-enterprise data model
  - Multi-enterprise master data management
  - Multi-enterprise security model
  - Multi-enterprise process flows
  - Rich set of multi-enterprise, networked applications
  - Integration of traditional systems and external data
  - Integration with other networks
  - Data veracity mechanisms and services to ensure ongoing high quality of data in the network
  - AI/ML algorithms trained on global, broadly representative multi-year data sets
- Network business model and policies
  - Effective incentives for participation across diverse range of trading partners and third parties
  - Value-based pricing for all participants
  - A set of shared, mutually acceptable identity-proofing policie

Hypothetical companies to illustrate typical benefits

For each scenario, we imagined a hypothetical "typical company" to illustrate what the typical benefits might look li e. The hypothetical company and the benefits th y may realize are briefly described in a series of sidebar boxes, using green text with green shaded background. The numbers and benefits presented are based on what an average or typical company might see. We start with a description of the company, as explained in the fir t side bar below.

Hypothetical Company Inc.

For each scenario, we describe a hypothetical company in a sidebar that looks like this. It will include some specifics about the type f business, products or services offered, and relevant business statistics such as revenue, profitabilit , and so forth.

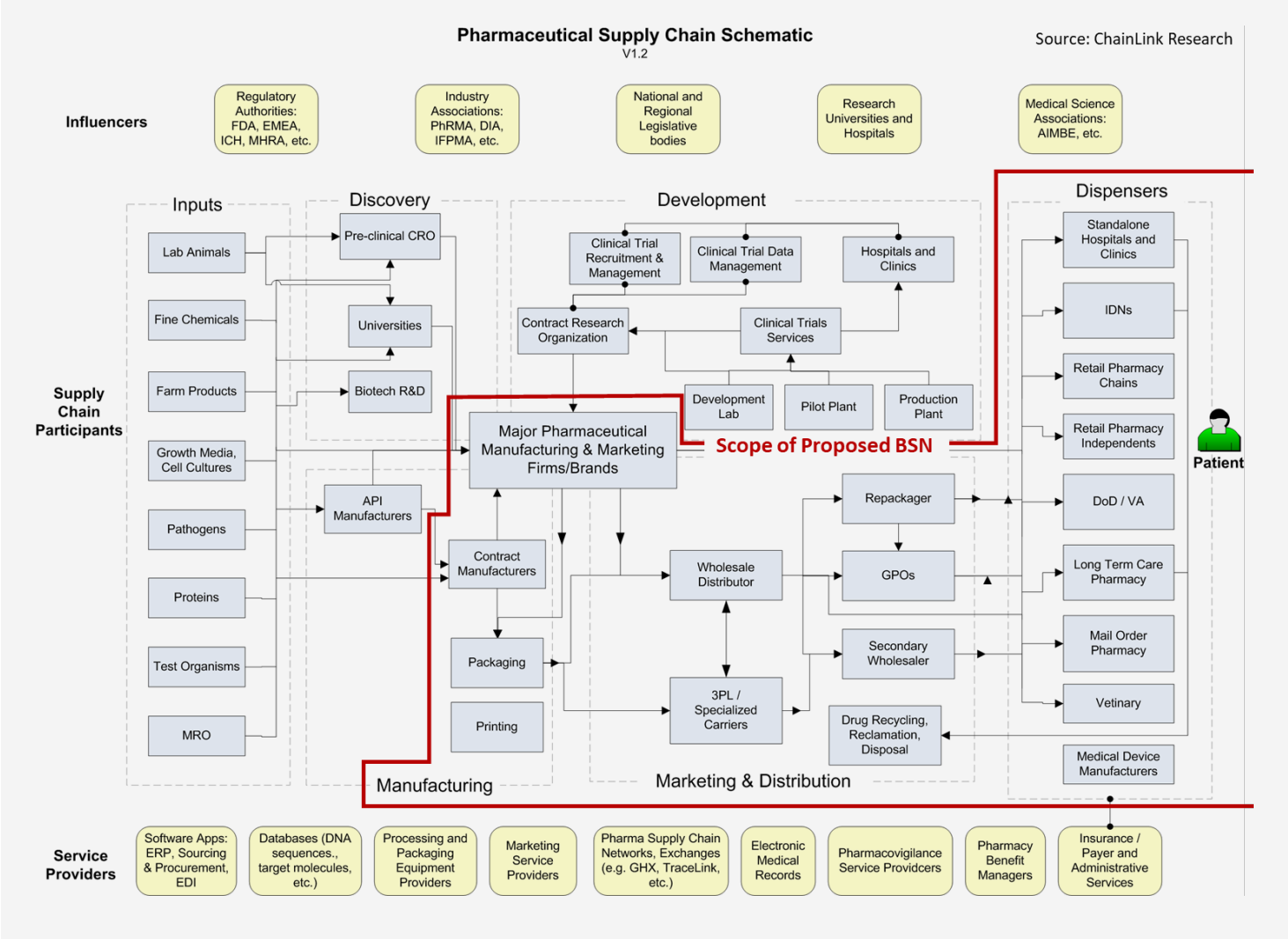

Figure 2 – The pharma supply chain has many participants

Pharmaceutical end-to-end chain-of-custody

Pharmaceutical supply chains: complex and challenging

Our fir t hypothetical BSN provides end-to-end chain-of-custody functionality for pharmaceutical supply chains. Pharmaceutical supply chains are complex, with many participants. At a high level, supply chain participants operate in one or more of the following functional segments: 1) *inputs*—companies providing the input materials (e.g., active pharmaceutical ingredients (APIs), excipients, diluents, binders, etc.), 2) *discovery*—those involved in R&D and discovering new treatments, 3) *development*—those developing drugs, conducting clinical trials, and shepherding the drugs through the regulatory approval process, 4) *manufacturing*—those firms manufacturin , packaging, and marketing the drugs, 5) *distribution*—those companies distributing drugs from the manufacturer to the dispensers, 6) *dispensers*—those dispensing the drugs to patients (including retail pharmacies and various healthcare providers), 7) *patients*—perhaps the most important segment, as the whole chain exists to serve and treat them. In addition to these seven supply chain segments, critical and highly influential roles are played by various service providers, payers, regulators, and industry groups.

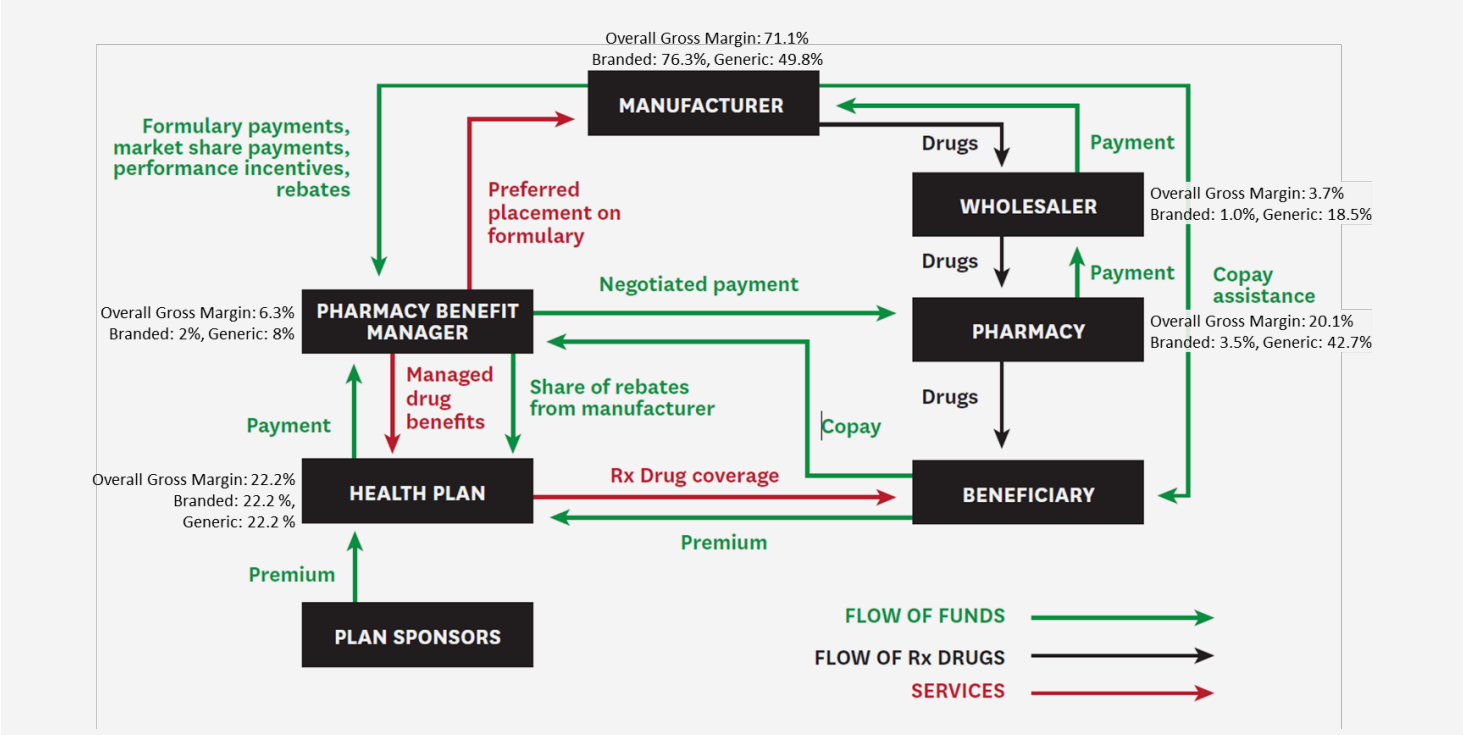

Figure 3 – Margins and flow of payments, drugs, and services in pharmaceuticals

The pharmaceutical supply chain faces many challenges, some of which can potentially be alleviated by a blockchain-based end-to-end chain-of-custody solution:

– *Diverse and conflicting incentives*—In addition to the typical set of conflicting interests[3] between trading partners, pharmaceutical supply chains have a set of unique characteristics and conventions that create some industry-specific, wide y varying, and often conflicting incentives for players up and down the chain. This often results in suboptimal supply chain decisions. For example, there is enormous variance between the margins earned by different types of players. Gross margins for pharma manufacturers are on average 71.1%, for wholesalers only 3.7%, and for pharmacies 20.1%.[4] To bring a single drug to market, manufacturers can invest over a billion dollars and take more than a decade of effort. In contrast, wholesale distributors have no investment in developing the drug, but make major capital investments in warehouses, IT systems, and developing various expertise.[5] These vastly different investments and margins lead to vastly different optimization strategies and decisions, such as deciding the optimal inventory level by location for each drug. Manufacturers earn much higher margins on branded drugs than on generics, but for wholesalers and pharmacy benefit mana ers (PBMs), it is reversed—the margins on generics are much higher.[6] A chain-of-custody blockchain network will not change these fundamentally different incentives, but it provides much better transparency and precise visibility of the flow of pharmaceuticals through the network, helping the various players better understand the consequences of their decisions and collaborate better to realize supply chain-wide improvements.

– *Financial complexity*—The pharma industry has a byzantine and ever-changing set of payment flows, parts of which are opaque, contributing to enigmatic (and sometimes perverse) incentives for different players. This has been exacerbated by the rise in power and changing role of PBMs (as well as group purchasing organizations (GPOs) and pharmacy services administration

[3] Virtually all supply chains have the usual "standard set" of conflicting interests for things like price ("I want to sell for more, you want to buy for less"), terms ("I want to get paid today, you want to pay me six months from now"), and inventory ("The other guy should hold the inventory."). These are typically negotiated based on the relative power position of the players.

[4] According to the USC Schaeffer (Sood 2017)

[5] Wholesale distributors invest heavily in building up expertise, systems, and processes in areas such as procurement, demand management and forecasting, distribution and logistics, and financial mana ement.

[6] For manufacturers, the COGS (Cost of Goods Sold) on branded drugs is less than half of that for generic drugs and less than a quarter of their selling price. In stark contrast, wholesalers' gross margin for generic drugs is about 18 times their margin on branded drugs (Comer 2019).

organizations (PSAOs),[7] an obscure flow of rebates, and in the US, a patchwork of state pharmaceutical regulations as well as a seemingly endless flow of ideas for new regulations and pricing mechanisms[8] to try to lower prescription drug costs. A chain-of-custody blockchain network could be extended to illuminate financial fl ws as well.

– *Distribution complexity*—The distribution path a shipment of drugs takes from the manufacturer to the dispenser can be highly circuitous, changing hands through a dozen or more different parties, especially outside of the US. In the US, about 90% of drugs flow through the three main national wholesale distributors, but there are still several regional wholesalers and almost 7,000 secondary wholesalers. Globally there are about 300,000 wholesalers[9] who constantly buy and sell from each other to meet current market demand, frequently stripping off original packaging and repackaging products in the process. This can create all kinds of challenges, such as grey market diversion, injection of counterfeits into the supply chain, and cold chain excursions. A chain-of-custody blockchain network can help solve these kinds of problems.

– *Intense regulation*—As one of the most highly regulated industries, pharmaceutical manufacturing is facing a set of deadlines for compliance with the US Drug Supply Chain Security Act (DSCSA) and similar supply chain regulations worldwide. A blockchain-based chain-of-custody solution is ideally suited to help companies provide the end-to-end traceability mandated by these regulations. More broadly, regulation requirements make it more difficu t for pharmaceutical companies to change processes and procedures up and down the chain, constraining changes to everything from manufacturing batch sizes to procedures for handling of drugs in transit to packaging changes. An industry-standard blockchain solution could help the industry make progress along many dimensions, while reducing the regulatory compliance burdens for each individual participating company.

– *Perishable, condition-sensitive products*—The market share of biologics is predicted to continue to rise rapidly.[10] These drugs are usually temperature sensitive, often with short shelf lives and/or other environmental sensitivities. This temperature sensitivity applies as well to the raw materials (APIs) and work-in-progress (WIP) inventory. Furthermore, about half of drugs are moisture- or humidity-sensitive[11]. A chain-of-custody solution that includes temperature and condition monitoring can help manage environmental conditions across the many players in the supply chain.

– *Patient adherence*—Patient non-adherence is a perennial problem. Research shows that 20% to 30% of prescriptions are never fi led, and about 50% of drugs for chronic illnesses are not taken as prescribed (Viswanathan, et al. 2012). In the US, non-adherence leads to an estimated 125,000 deaths and added healthcare costs of $100B-$300B annually (Viswanathan, et al. 2012). The economic cost of lost productivity is estimated to average 2.3 times those added healthcare costs (Healthentic 2015). Diverse interventions used to try to improve compliance include better drug packaging design, case management and counseling, education and coaching, reminders, and other decisions aids. The move to outcome-based pricing will provide even more motivation for drug companies to get involved in improving patient adherence. A true end-to-end chain-of-custody solution, going all the way to the patient, could add a set of tools for monitoring and encouraging compliance.

[7] PBMs negotiate the formularies that heavily influence which drugs are consumed. GPOs aggregate purchases for providers and pharmacies. PSAOs provide tools and services to pharmacies, including negotiating contracts with PBMs and payors.

[8] There has been a longstanding broad push for value-based pricing, a fundamental change that has been slow to realize in practice, but which is starting to take hold (enabled in part by wider adoption of electronic health records). New pricing models dramatically reshape the incentives for pharma manufacturers. These models include financial ris -based contracts, health outcomes contracts, mortgage models, subscription models, and indication-specific pricing (Comer 2019)

[9] Source: (Dun and Bradstreet 2021)

[10] One source shows the market share of biologics in high-potency active pharmaceutical ingredients rising from less than 22 percent in 2015 to 25% in 2020 to almost 29% by 2025 (Grand View Research 2017). Other sources show slightly lower numbers for biologics as a percent share of the pharmaceuticals market, but with very similar market share growth rates. subscription models, and indication-specific pricing (Comer 2019)

[11] Too low humidity creates static charges that can dry out medications, affect solvents, and cause crumbling or sticking. Too high humidity can compromise efficacy or ven lead to toxicity. (Colorcon 2020)

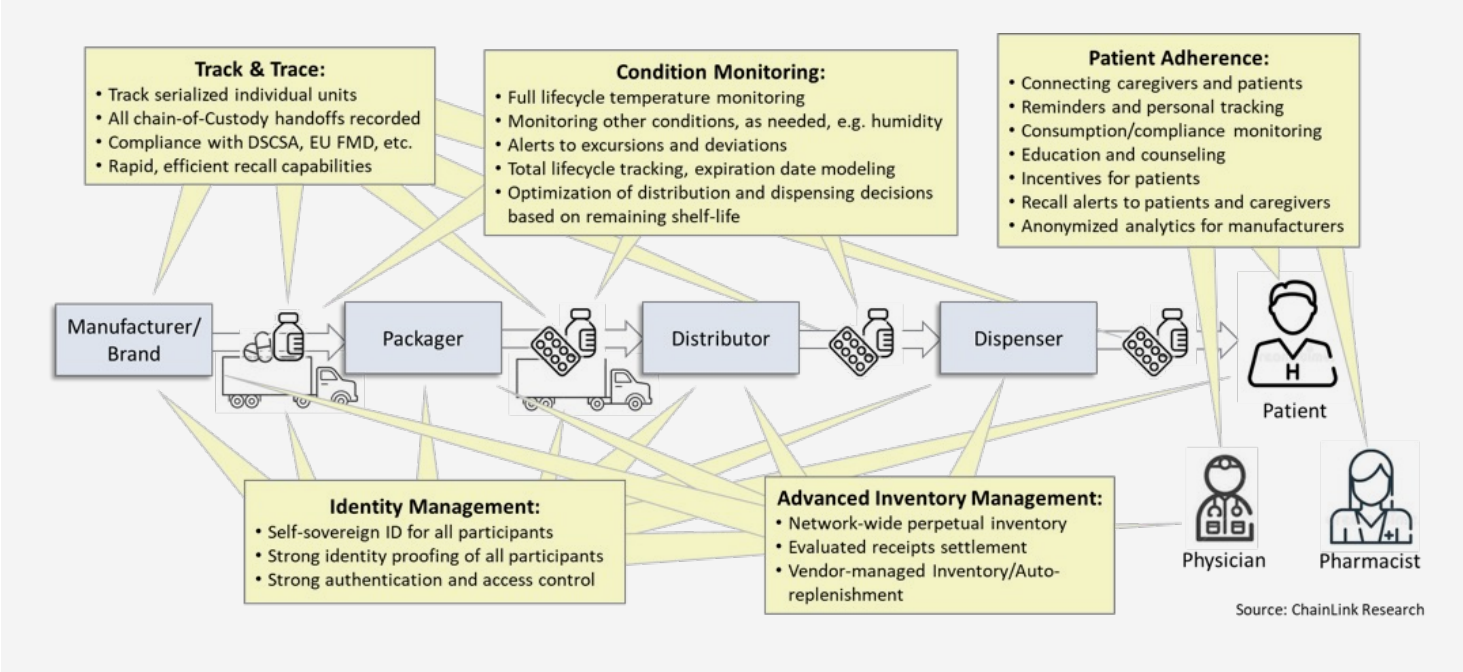

Figure 4 – Proposed PharmaNet functionality

A "produce-to-use" chain-of-custody solution

A "produce-to-use" chain-of-custody solution tracks and monitors pharmaceuticals all the way from the point of production ("produce") to the point of consumption ("use") by the patient. This is inherently a multi-enterprise and multi-entity solution, as it involves manufacturers, packagers, distributors, logistics service providers, dispensers, and the patients themselves. A BSN is well suited to support chain-of-custody management across multiple parties. In Figure 4 we envision a BSN offering fi e main areas of functionality. We refer to this hypothetical chain-of-custody BSN as "PharmaNet."

– *Identity management*—While virtually all B2B BSNs require strong identity management, the need is especially acute in pharmaceutical networks, where highly confidential dat [12] is being shared. Blockchain technology provides a foundation for verifiable c edentials and self-sovereign identity, which are key pieces of the distributed network security puzzle. A lot of work on these has already been done.[13] The services provided by the network would include identity proofin , authentication, and access control.

– *Track and trace/recall*—The platform would provide end-to-end traceability, providing network-accessible records of each chain-of-custody handoff. This will help companies comply with DSCSA and other regulations around the world.[14] This type of system will have benefits including po entially dramatic reductions in counterfeits and grey market diversion, much more rapid, precise, and less costly recalls. The platform also provides the ability to reinforce contractual obligations,[15] which further curtails grey-market sales and counterfeits. It provides mechanisms to encourage dispensers to participate and tools for them to record all dispensing of the drugs being tracked, as well as tools for patients and caregivers to record patients' consumption of those drugs. That information could be used to notify specific dispenser , caregivers, and patients in case of a recall.

[12] Confidentiality is pa ticularly critical for discovery and clinical trial phases, but it is also important to protect all the transactional data, and especially the individual patient data, that is maintained by the network we are describing here.

[13] For example, the non-profit Sovrin Foundation provides technical standards and governance for many SSI implementations. Another example, IBM Digital Health Pass is a blockchain-based service providing verifiable hea th credentials to certify COVID vaccinations and test results, allowing the certifica e holder to travel, enter venues and engage in activities.

[14] The DSCSA (Drug Supply Chain Security Act) mandates end-to-end traceability for drugs sold in the US by 2023. Argentina, South Korea, the Russian Federation, and Turkey have all enacted similar regulatory requirements for end-to-end traceability. The EU's Falsified Medicines Di ective currently mandates registration of serialized units (with tamper-evident packaging) at the EU Medicines Verification Hub, thereby providing point-of-dispensing verification, but some xpect the EU to include end-to-end traceability in future regulatory requirements.

[15] Specifica ly, the envisioned platform would provide reminders and communication of contractual obligations requiring authorized dealers to only sell to and source from other authorized dealers, up and down the chain. As well it would provide education, tools and reminders of contractual clauses committing dealers to implement processes to consistently record all sales and chain-of-custody handoffs on PharmaNet, thereby establishing unbroken end-to-end tracking.

– *Inventory management*—End-to-end track and trace provides a foundation for network-wide perpetual inventory management, evaluated receipts settlement, and vendor-managed inventory (VMI). The network-wide perpetual inventory system is not intended to replace existing inventory systems for most participants.[16] The network provides evaluated receipts settlement. When a shipment is received and confirmed o be in good order, a payment is automatically scheduled without any invoice needed.[17] With VMI, the system provides tools for the supplier to monitor inventory levels and replenish stock to maintain agreed-to inventory levels (per contract) without the buyer having to issue a new order each time.

– *End-to-end cold chain/condition monitoring*—The envisioned network platform would provide end-to-end temperature monitoring, from the point of manufacturing to dispensing. This will include alerts for temperature excursions (and potentially other environmental condition deviations, such as excessive humidity), with analytics that track total lifecycle exposure to calculate the impact on drug efficacy or emaining shelf-life. Remaining shelf-life estimates can be used to optimize distribution and dispensing decisions, thereby minimizing loss of expired product while ensuring efficac .

– *Patient adherence*—The vision for the platform is that chain-of-custody does not stop at the dispenser, but rather goes all the way to the patient including (with informed consent) tracking the actual consumption of the drug by the patient. Further, the network connects caregivers as well to help ensure the desired outcome. The platform service would provide patients with an app that provides reminders, education, personal tracking, and monitoring.[18] The monitoring could involve QR code scans, smart pill bottles or packages, or possibly even ingestible sensors.[19] The app is connected to the network, allowing involvement and interaction between the patient and the primary care and specialist physicians, pharmacists, case workers, and counselors. Ideally, financial and other incentives are interwoven into the solution, possibly funded by insurers. Because the drugs are serialized down to the end-unit level, recall alerts can be directly delivered to the patient and caregivers, advising of actions that need to be taken, such as disposing and replacing remaining doses. On the back end, analytics can be used to provide outcome tracking to manufacturers, caregivers, and researchers. Valuable anonymized information can be provided to help these parties understand adherence rates and correlated outcomes.

– *Interoperability and Integration*—PharmaNet will be designed assuming that many of the companies participating on the network will already use other networks or systems to implement some of the same functionality that BSN provides. For example, some companies may be on other networks that provide DSCSA-compliant traceability, or cold chain functionality, or combinations of other functionality. Because of this, PharmaNet will provide comprehensive interoperability with other popular networks as well as integration with commonly used enterprise systems. It will be architected in a way that each participant can decide exactly how to meld their existing functionality with PharmaNet functionality. The dividing line between what functionality is performed on PharmaNet vs. on other networks and systems will be highly granular and flexible (small chunks of functionality can be moved from one to the other) and unique for each participant. That dividing line can evolve over time. For example, the customer can retire some existing systems and move that functionality onto PharmaNet.

The capabilities described above are broad and ambitious. In a practical scenario, the network would most likely start with a focused subset of these capabilities. For example, the platform might fir t focus on DSCSA compliance. Once it was gaining traction, with a critical mass of adoption and funding or revenue, it could start to expand into other areas, prioritized by the network participants' needs and market demand.

[16] For participants that currently do manual inventory management, the network provides a simple inventory management system that could replace their paper-based systems. For those that have electronic inventory systems, it provides mechanisms to reconcile any differences between their company's own inventory numbers and the network's numbers.

[17] Evaluated receipts settlement is possible because the platform already knows exactly what was ordered and what was shipped and what is in the contract. Payment is automatically calculated based on the agreed-to terms and pricing in the contract.

[18] Over time, the app could be expanded to include other patient healthcare-related functionality, such as tracking of other health metrics (e.g., blood pressure), medical history repository, wearables integration and so forth. The secure foundation of the blockchain network, combined with robust security practices, should help build the trust required for patients to decide to store sensitive information on the network.

[19] In 2017, the FDA approved the fir t drug in the US with a digital ingestion tracking system. Due to their privacy invasiveness, these types of technologies should be done only with robust informed consent, ensuring the patient understands what they are agreeing to and does not feel pressured to consent. Further research is needed to better understand the effectiveness of these kinds of invasive monitoring vs. other adherence interventions.

Value generated by an end-to-end chain-of-custody BSN

Summary of value realized by BioPharma Inc. using PharmaNet
Here we estimate the potential value generated through use of the envisioned PharmaNet by our hypothetical company, BioPharma, Inc. The total value realized by our hypothetical $15B manufacturer, BioPharma Inc., is substantial, as shown in Table 1. It includes increased revenue of over $1.2B, increased profits f nearly $290M, and $140M of working capital freed up for other uses. This represents a high ROI, even assuming a cost of $10M to $20M per year for using PharmaNet[20] and implementing the programs described in following sections.

BioPharma Inc.
BioPharma Inc. is a hypothetical global biopharmaceuti-cal company with 10,000 employees and revenue of $15B. It develops and commer¬cia¬lize biologics, many of which require tempera¬ture-controlled handling. Gross margins are 73% and net margins are 13%, resulting in $1.95B of net profit. Expec ed benefits or BioPharma Inc. from its participation in PharmaNet are described in following sections. These benefits a e further detailed in the green sidebars labeled *"BioPharma Inc. hypothetical impact."*

Revenue	*Patient Adherence:*	5% reduction in unfullfi led prescriptions	$ 1,000 M
	Ease-of-Doing-Business:	Increased revenue from enabling evaluate receipts settlement, auto-replenishment, reduced shortages	$ 150 M
	Anti-counterfeiting:	30% reduction in counterfeiting	$ 90 M
		Total Increased Revenue	**$ 1,240 M**
Cost Reductions/ Profit Increase	*Evaluated Receipts:*	Eliminating invoice issuing	$ 8 M
	Expired Drugs:	25% reduction in expired drugs returned	$ 40 M
	Cold Chain:	20% reduction in excursions and lost product (COGS saved), and excursion-related process costs	$ 39 M
	Grey Market:	Profits ecovered by 50% reduction in grey market sales	$ 38 M
	Recalls:	Reduced cost of recalls	$ 15 M
		Total Pharma Supply Chain Cost Reduction/Increased Profit	**$ 140 M**
Compliance	*Regulatory Compliance:*	Value of regulatory compliance	$ 1.5 M
		Total Value of Compliance Delivered	**$ 1.5 M**
Working Capital	*Inventory management:*	7% reduction in DIO while maintaining service levels	$ 140 M
		Working Capital Freed Up	**$ 140 M**

Table 1 – Estimated value realized by a hypothetical company, BioPharma Inc., via comprehensive use of PharmaNet

[20] The assumption here is that BioPharma Inc. would not be convening the BSN, but rather using a BSN convened by someone else and paying the convener a set of recurring fees.

The next 10 pages describe how these estimates of value are derived. They include descriptions of the how the PharmaNet functionality drives the benefit, ey metrics for measuring value, mechanisms of improvement, range of expected improvement, and value calculations. If you want to skip these details, feel free to skip forward to the section *Value for other pharmaceutical supply chain participants*.

The following detailed descriptions of how value is generated are organized into four categories:

– *Patient outcomes*—This section describes how the patient adherence functionality leads to better patient outcomes. Reductions in the number of unfulfi led prescriptions drive increased revenues.

– *Ease of doing business*—This section discusses four ways that PharmaNet increases ease of doing business: 1) *receiving process and evaluated receipts*—labor savings from eliminating the issuing and processing of invoices; upon confirmation of receipt of goods by the buying party, payments are automatically scheduled, 2) *automatic-replenishment*—Labor savings by automatically replenishing inventory when stock falls below a certain level, 3) *inventory management tools*—Simple tools for smaller healthcare providers and independent pharmacies to manage their inventory, 4) *shortages management*—Labor savings and improved outcomes via reduced shortages.

– *Inventory management*—This section describes reducing inventory levels while maintaining or improving service levels through the better visibility and more optimized deployment of inventory enabled by PharmaNet. Reductions in expired drugs and returns increase revenues.

– *Compliance and control*—This section covers several areas: reduction in counterfeits and grey market diversion; reduction in loss due to temperature excursion via improved cold chain management; compliance with new serialization and end-to-end traceability regulations; and lower cost of recalls.

The following sections focus on these benefits or a pharmaceutical manufacturer, as embodied by our hypothetical company, BioPharma Inc. However, PharmaNet generates value for all supply chain participants, as discussed briefly in the section *Value for other pharmaceutical supply chain participants.*

Patient outcomes

Patient adherence

Patient outcomes are the ultimate purpose of the healthcare system. Improvements to outcomes may be the most ambitious goal of the envisioned PharmaNet platform. There are several ways in which PharmaNet improves patient outcomes. The biggest impact comes from improving patient adherence, which is the focus of this section. Following sections describe some additional ways the platform improves outcomes, such as reducing drug shortages (covered in *Ease of doing business*) and reducing undetected excursions for temperature-sensitive drugs (covered in *Compliance and control*).

The envisioned PharmaNet improves patient adherence by providing patients with an app that includes reminders, education, personal tracking, monitoring of consumption, and counseling or remote interaction with the patient's primary care doctor, pharmacist, and counselors. The app also provides drug recall alerts and instructions. Fully anonymized data about patient compliance is provided to manufacturers to help them understand adherence rates and correlated outcomes. A complete patient adherence initiative of the type envisioned here requires the integration of healthcare providers, drug packaging and delivery systems, the development of related educational and counseling materials and programs, and ideally insurance-funded incentives for patient compliance. This requires a multi-party investment that the PharmaNet convener could coordinate. Healthcare providers, insurance companies, pharmacists and drug manufacturers should all be willing to invest in a system that delivers results, as lack of adherence is costly to all of them.

The platform's capabilities primarily impact two adherence-related metrics: 1) unfulfi led subscriptions, and 2) improperly consumed drugs. About 20% to 30% of prescriptions remain unfi led (Viswanathan, et al. 2012). The most common reason patients fail to fi l their prescriptions is the high costs. Because of this, reducing subscription abandonment rates disproportionately impacts the most expensive drugs (i.e., patent-protected), thereby lifting margins as well. Other reasons for not fi ling prescriptions include fear of undesirable side effects and simply not wanting to take the drugs. The platform, together with the patient's caregivers connected on the platform, actively intervene to solve these problems, such as prescribing a lower-cost alternative drug or one without the specific ffending side effects, as well as helping the patient understand the consequences of not taking the drug and coaching on how to mitigate side effects. We estimate that the platform, integrated with a program incorporating the envisioned interventions, could reduce unfulfi led subscriptions by 10 to 50%.

Research indicates that about 50% of drugs for chronic diseases are not taken as prescribed (Marie T. Brown 2011). This can include skipped doses, taking medications at the wrong time or quantities, and other problems. The platform notifies ca egivers

of nonadherence so they can intervene[24] appropriately. It also can provide reminders, alerts, educational materials and so forth directly to the patient. Studies have shown that behavioral and educational interventions can improve adherence by 4% to 11%. Some interventions are even more effective; for example, changing the frequency of a drug's dosing from four times a day to once a day improves adherence on average by almost 30% (Marie T. Brown 2011). Improving how often drugs are taken as prescribed improves outcomes, often dramatically. For example, when stent recipients discontinued their thienopyridine therapy (by their own non-adherence, not due to advice of their physician), their mortality rate after one year was 10 times higher than those who continued the thienopyridine therapy (7.5% vs 0.7%) (Marie T. Brown 2011). If current rates of non-adherence were cut in half, it would save the US healthcare system an estimated $50B - $150B per year and add $120B - $350B of productivity back into the economy.[25]

Ease of doing business

Many factors (such as price and drug efficacy) influen e which drugs PBMs, GPOs, and healthcare providers select. Ease of doing business is one of those factors that comes into play. PharmaNet provides a number of capabilities that make things easier for pharmacies and healthcare providers, and the PBMs, GPOs, and distributors that supply them. This makes them more likely to buy drugs via the PharmaNet network. The ease of doing business that a PharmaNet would provide include:

– *Streamlined receiving and invoicing processes*—The blockchain network records physical events around movement of goods, creating a shared, trusted source of truth that can be used to streamline receiving and invoicing processes, such as by implementing evaluated receipt settlement (ERS), which eliminates non-value-add invoicing and reconciliation tasks. When a shipment is received, the platform already knows exactly what was ordered and what was shipped. The receiving party confirms that the i ems were received in good condition, ideally via an unforgeable scan (e.g., RFID or barcode) of the goods. Normally at this point, the supplier issues an invoice that the buyer's AP department checks and reconciles before issuing a payment. With evaluated receipts settlement, those steps are eliminated. Instead, a payment is automatically scheduled, according to agreed-to terms, based on the existing contract and VMI pricing agreement, taking into account any volume discounts. This saves a lot of manual labor and disputes for both parties.

Patient adherence and outcomes

– *Key metrics:*
  - percentage of prescriptions unfi led
  - Adherence rate
  - Remission and recrudescence rates
  - percentage of readmissions (7-day, 30-day)
  - Mortality rate (1-year, 5-year)
– *Improvement mechanism:*
  - The combination of alerts, education and intervention provided by the platform increases prescription fulfi lment rates and patients' adherence to the prescription regime.
  - Increased adherence results in lower recrudescence, readmissions, mortality and other measures of outcomes.
  - Better outcomes result in lower overall medical costs.[21]
  - Increased prescription fulfi lment results in higher revenues for manufacturers, distributors, and pharmacies, especially for their higher-priced drugs.
  - Improved outcomes lift revenue and margins whenever outcome-based contracts are used.[22]
– *Typical improvement range:*
  - We expect the rate of unfulfi led prescriptions to be reduced by 10% to 50%. For example, if the current rate of unfulfi led prescriptions is 25%, it could be reduced to between 12.5% to 22.5%.
  - We expect adherence to be improved by 5% to 30%.
  - Improvements to recrudescence, readmissions, mortality, and other measures of outcomes vary widely, but can be 10X or more for compliant vs. non-compliant patients.

BioPharma Inc. hypothetical impact

- The rate of unfulfi led prescriptions for BioPharma Inc. is reduced from 25% to 20%, resulting in a 6⅔% increase[23] in revenue = $1.0B.

BioPharma Inc. realizes a $1.0B increase in revenue, due to 5% fewer unfi led prescriptions. They are also selected more often as the drug provider of choice, because they provide tools that increase adherence rates, thereby improving outcomes and reducing overall healthcare costs.

[21] The impact on providers' revenue depends on whether their revenue model is volume-based (per-unit model) or value-based (outcome model). A platform like PharmaNet can also be an enabler of value-based pricing by providing precise information about patient adherence, which can then be correlated to outcomes.

[22] Currently, outcome-based contracts are not widely used. When used, they are often for durable drug therapies, such as gene therapies, that can have lifetime benefit , for which dose prices are often astronomical. In those cases, adherence rates are expected to be virtually 100%. In the future, if outcome-based contracts become more prevalent and used more often with maintenance drugs, then manufacturers will become more incented to help improve adherence rates for those.

[23] Current revenue is 75% of what it would be if all subscriptions were fi led. Lowering the unfi led subscription rate from 25% to 20% raises revenue to 80% of the full potential. 80% = 75% X 106⅔%, thereby 6⅔% greater than current revenue.

[24] Interventions may be behavioral (e.g., simpler dosage schedule, skill building, rewards, reminders) or educational (providing information about the disease or medication).

[25] Based on estimates of drug non-adherence adding $100B - $300B annually to healthcare costs (Viswanathan, et al. 2012) and the economic cost of lost productivity averaging 2.3 times the added healthcare costs (Healthentic 2015)

– *VMI and automatic-replenishment*—Because the system is monitoring inventory levels, suppliers can automatically replenish inventory when stock falls below a certain level.

– *Inventory management tools*—The platform can provide simple inventory management tools to healthcare providers, independent pharmacies, and others in the supply chain that may be currently managing inventory using manual, paper-based processes. These systems have the advantage of being fully pre-integrated into the network.

– *Shortages management*—After falling for fi e years in a row (2011 - 2016), drug shortages have been on the rise since 2017. According to the FDA,[26] 62% of shortages (in 2019) were due to quality issues, 12% due to increase in demand, 5% from natural disasters, 3% from discontinuation of production, and 18% "unknown." Many aspects of the market structure disincentivize manufacturers to invest in addressing shortages. The envisioned PharmaNet does not materially address these structural issues, but nevertheless can help somewhat in reducing shortages and their impact. The PharmaNet we describe here does not provide inbound supply chain disruptions visibility for manufacturers, which would be one element of addressing shortage issues. However, it provides wholesalers and dispensers better visibility into available finished oods supply across the network, as well as providing manufacturers with better visibility into demand surges. More accurate near-term and mid-term forecasting allows earlier adjustment to deviations from plan and more accurate inventory optimization calculations (getting limited supply to where it is most needed). This enables the platform to reduce a portion of shortages. The platform also provides coordination and communication mechanisms between different healthcare providers, distributors and manufacturers to execute a more coordinated chain-wide response. As well, the platform would include tools to help communicate and update clinical guidelines, including policy recommendations (such as prioritization policies), alternative treatments, and threat analysis tools (assessing the duration of the shortage, for example). For many manufacturers (especially those providing patent-protected drugs), shortages do not have a significan impact on their revenue or profit. H wever, shortages have a material impact on the cost and efficacy f care for care providers. Thereby, tools that limit the scope and impact of shortages will be welcomed by care providers and may influence which manufacturer becomes a preferred supplier.

Auto-replenishment, shortages management

– *Key metrics:*
  • Replenishment and invoice processing cost
  • Dispute management cost
  • percentage of drugs in shortage
  • Shortage-related costs
  • Shortages impact on patient outcomes
  • Manufacturer's share of business
– *Auto-replenishment improvement mechanisms:* All receipts of drugs into and withdrawals from dispensers' stocking locations are recorded and securely maintained on the network and fed into transparent auto-replenishment algorithms. The network forecasts needs and requests suppliers to plan future production and shipments to fulfi l auto-replenishment orders. This saves the dispensers labor for inventory counting and replenishment ordering and reduces stockouts.
– *Evaluated receipts settlement:* Eliminates invoice processing costs and disputes.
– *Shortage improvement mechanisms:* Early, detailed visibility into demand surges enables earlier, better production and distribution planning to reduce shortages. Visibility into network-wide inventory allows rebalancing of limited inventory across the network to serve the areas of greatest needs. Better expiration management reduces shortages. Better communications between providers and distributors, as well as sharing of policy recommendations, enables more effective use of limited supply. Reduction in shortages and better intelligence from the network results in fewer procedure cancellations, reduced medication errors, and less labor managing critical drug lists and sourcing from nontraditional channels. Patient outcomes are improved because the right drugs are available at the right time.
– *Revenue increase mechanism:* The combination of auto-replenishment benefits (labor s vings, fewer stockouts), evaluated receipts settlement (no invoice processing, reduced disputes), and shortage benefits (labor s vings, fewer cancellations and medical errors, improved patient outcomes) together make the manufacturer that delivers those benefits a p eferred provider, thereby driving increased revenue for them.
– *Typical improvement range:* 0.5% to 5% increased revenue.

BioPharma Inc. hypothetical impact

• 1.0% increase in revenue = $150M.

By implementing PharmaNet, BioPharma Inc. becomes a preferred supplier, increasing revenue by $150M.

[26] Per the FDA's Seventh Annual Report on Drug Shortages for Calendar Year 2019 (U.S. Food & Drug Administration 2020)

Estimating the impact that ease of doing business has on a pharmaceutical manufacturer's revenue is challenging.[27] For those making the buying decisions (PBMs, GPOs, pharmacies, healthcare providers), many factors go into selection of one drug (or provider) over another. Providing streamlined receiving and payments processes, inventory management tools, and auto-replenishment should help specific drug manufactu ers become the preferred providers for hospitals and pharmacies. Better shortages management, coupled with some type of service level agreement (SLA) commitment, could also make particular manufactu¬rers more desirable to the ultimate buyers. Together, we estimate these ease-of-doing-business capabilities could add 0.5% to 5% to a drug maker's revenue.

Inventory management

- *Key metrics:*
  - Days inventory outstanding (DIO)
  - Cost of goods sold (COGS)
- *Improvement mechanism:* Much better end-to-end inventory, consumption and supply visibility enables faster and more accurate responses to demand variation and supply disruptions.
- *Typical improvement range:* 5% to 10% reduction in DIO

Optimized inventory management

The PharmaNet network provides mechanisms to better optimize available inventory, thereby freeing up working capital and reducing expired product.

The average amount of inventory held by major pharmaceutical manufacturers is quite high, about 180 days inventory outstanding,[28] much higher than other industries such as CPG companies (~60 days) and high-tech electronics (65 - 70 days). There are many valid reasons for pharmaceutical manufacturers to hold higher levels of inventory than other industries.[29] Margins for pharmaceutical firms h ve traditionally been much higher than other industries (especially for branded drugs) and the impact of shortages more dramatic, leading to more of an emphasis on ensuring supply rather than reducing inventory. However, several trends are putting pressures on margins, such as patent cliffs, the rise of generics, and downward price pressure from powerful payors. As well, a shift from blockbuster drugs to personalized medicine, genomics, and orphan drugs has led to proliferation of SKUs and supply chain complexity. These are all driving increasing importance of managing excess inventory levels.

PharmaNet provides end-to-end visibility into inventory levels and near-real-time consumption across the supply chain. This enables manufacturers and distributors to detect deviations from demand plans sooner. As well, it allows analytics that can spot mismatches between what is being produced, where it is being stocked, and where there are shortages. This allows production and distribution that more closely matches actual consumption. Thus, the supply chain can provide higher service levels (fewer shortages) while simultaneously reducing inventory levels. By better aligning production and distribution with consumption, we estimate that inventory levels could be reduced by 5% to 10%, without negatively impacting revenue or service levels (shortages).

BioPharma Inc. hypothetical impact

- COGS = 27% ≈ $4B
- Current DIO: 180 days ≈ $2B
- 7% reduction in DIO ≈ $140M

In this scenario, the visibility brought by the BSN frees up $140M of working capital.

[27] While cross-industry research suggests that non-price factors outweigh price in determining market share, we found a dearth of research on the impact to pharmaceutical revenue from ease of doing business.

[28] According to a 2010 report by McKinsey, *"The average pharmaco holds 180 days of finished goods inventory on hand."* (David Keeling 2014). A 2017 report by nVentic (nVentic 2017) said *"Median inventory levels for the industry are high - ~180 days DIO"*. A 2019 report by nVentic (nVentic 2020) showed that inventories had grown since 2017. These numbers belie the enormous range of inventory held by major pharma companies, from ~80 days to over 320 days.

[29] Pharmaceutical manufacturers are challenged to reduce inventory in a prudent manner due to many factors such as: high service level requirements (hospitals and pharmacies never want to be out-of-stock for critical medicines), regulation-imposed batch size requirements that cannot be easily changed, long production times, perishable products, patent expiration deadlines, and limited number of suppliers for key ingredients.

Reducing expired drugs

About 1.5% to 2% of drugs sold are returned to the manufacturer for credit, with 72% of those returns due to product expiration (outdated or short dated). The PharmaNet would provide highly granular, near-real-time visibility across the entire supply chain to help identify where in the supply chain expirations are occurring and help diagnose why they are occurring. Armed with this information, manufacturers, wholesalers and dispensers can work together to reduce expirations through a variety of means,[30] such as:

- Ensuring pharmacies are inspecting and rotating stock, as well as transferring aging inventory to more actively dispensing locations.
- Alerting distributors and dispensers to shorter-life product, so they can take proactive action.
- Holding back more inventory at distribution centers to better respond to end-of-season demand fall-off, sending product to where it will be consumed.
- Rationalizing SKUs based on demand and sourcing slow movers via wholesaler or direct from manufacturer.
- Better coordinate new product delivery with prescriber communications; provide complete lifecycle instructions; evaluate new product demand early to rebalance production and inventory levels.
- Better align product packaging unit counts with common prescribing practices.
- When patent expiration dates are coming up and competing generics will be launched, doing more granular and accurate monitoring of branded product inventory levels at all locations across the network.

Taken together, we estimate these measures could reduce returns by 20% to 50%. In addition to the reduction in credits issued, there are savings from reductions in reverse logistics and disposal costs.

Reducing expired drugs

- *Key metrics:*
  - Credits Issued for returned expired drugs as percentage of revenue.
- *Improvement mechanism:* The network provides much more granular, timely and complete (end-to-end) visibility about drug expiration dates. Intelligence is provided to 1) identify where expirations are occurring, 2) diagnose why expirations are occurring and 3) drive process improvements such as better stock rotation, transferring aging inventory to higher consumption locations, rationalizing slow-moving SKUs, improving product launch monitoring, and better management of inventory levels during patent expiration.
- *Typical improvement range:* 20% to 50% reduction in expired drugs.

BioPharma Inc. hypothetical impact

- Returns for credit = 1.5% = $225M
- Returns due to expiration = 72% = $162M
- Reduction in expired drugs = 25% ≈ $40M

In this scenario, the visibility brought by the BSN enables process improvements that reduce losses due to expired drugs by $40M, resulting in a $40M increase in net profit

Compliance and control

There are several ways that the platform improves compliance and control across the supply chain, including:

- *Anti-counterfeiting*—Counterfeits are reduced due to robust end-to-end chain of custody tracking.
- *Cold chain temperature excursions*—Excursions are reduced by a combination of chain-wide accountability, systemic improvements, real-time alerts and actions, and better-informed distribution and dispensing decisions.
- *Grey market diversion*—End-to-end chain of custody tracking reduces grey market diversion.
- *Regulatory compliance, recalls*—The platform provides compliances with DSCSA and similar imminent serialization and end-to-end traceability regulations. It also reduces the cost of recalls.

[30] Most of these recommendations, as well as the statistics regarding expired drugs, are from the HDMA report *"Understanding the Drivers of Expired Pharmaceutical Returns"* (HDMA Returns Task Force 2009)

Anti-counterfeiting

Counterfeit drugs are a serious issue with serious consequences for healthcare outcomes and expenses.[31] There is, however, little consensus about the size problem. Estimates of counterfeit drugs range from 2% to 10of all drugs sold worldwide. The range of market value estimates of counterfeits is even more extreme: from $4B to $431B. Based on our research, we estimate the size of the counterfeit drugs market is probably around $40B, equating to about 3% to 3.5% of the total global pharmaceuticals market (prescription + OTC). However, the rate of counterfeits is much higher in developing countries than in developed countries. About 75% of counterfeits are sold in developing countries, even though those countries buy only about 15% of the total drugs sold globally. Some estimates indicate that in parts of Asia, Africa, and Latin America, at least a third of the drugs sold are counterfeit.

The PharmaNet platform would provide track and trace of individual serialized units at every handoff in the chain of custody, from the manufacturer all the way to the dispensers and the consumers. This allows any party, at any stage (including the end consumer), to confirm that th y are receiving legitimate product. This visibility needs to be combined with robust monitoring and vigorous enforcement. Together, these could have a dramatic impact on reducing counterfeits. We estimate that using the PharmaNet platform to drive monitoring and enforcement programs could reduce counterfeits by 25% to 75%. Assuming legitimate drugs were sold instead, that would equate to recovery of about 0.8% to 2.5% of revenue for global pharmaceutical companies.

Cold chain temperature excursions

Biopharmaceuticals currently account for about a quarter of the global pharmaceutical market but are growing at about twice the rate of the market as a whole. Biopharmaceuticals are temperature sensitive. Their growth is leading to a corresponding growth in the need for cold chain services. The unprecedented scale of the COVID-19 vaccination effort has only accelerated this trend.

The pharmaceutical supply chain already employs a wide array of methods and services for cold chain logistics, including extensive services from major 3PLs, carriers, and distributors,

Anti-counterfeiting

- *Key metrics:*
  - Counterfeits sold as percentage of total sales.
- *Improvement mechanism:* End-to-end chain-of-custody tracking of individual serialized units enables verification f drug authenticity at each stage of the supply chain, all the way to the consumer. Vigorous enforcement, based on this visibility, reduces counterfeits.
- *Typical improvement range:* Reduction in counterfeit drug sales by 25% to 75%.

BioPharma Inc. hypothetical impact

- Currently counterfeits sold are equivalent to 2% of BioPharma's revenue = $300M of counterfeited products sold worldwide
- Counterfeits are reduced by 30% = $90M, using the PharmaNet.

BioPharma Inc. increases revenue by $90B by replacing counterfeit drug sales with genuine drug sales.

myriad varieties of dedicated temperature monitoring devices and services, and a wide range of cold-chain packaging and conveyance systems. Nevertheless, cold chain logistics are complicated, with many players handling a product on its end-to-end journey from manufacturer to patient. As a result, temperature excursions occur too often. Estimates of the rate of excursions vary widely (from 1% to 25%).[32] One study (Barrowclough 2020) estimated the cost of temperature-related issues for pharmaceuticals at around $35 billion annually, from a combination of lost product, clinical trial loss and replacement costs, wasted logistics costs, and the costs of root-cause analysis. Of this, about $15 billion per year (a little over 1% of revenue), is the cost of lost product from cold chain failures (Cece 2020).

[31] Most articles and reports tend to overstate the extent of counterfeit drugs. They have an agenda to bring attention to the issue of counterfeits and as a result they too often seek the highest numbers and most attention-grabbing interpretation of those numbers that they can find. or example, a common misleading fi ure, often attributed to the WHO (World Health Organization), is that 10% of drugs globally are counterfeit. The 2017 *WHO Global Surveillance and Monitoring System for Substandard and Falsified Medical Products* report said *"the observed failure rates of substandard and falsified medical products in low- and middle-income countries at approximately 10.5%"*. However, this number is only for the developing world, which accounts for about 15% of the global drugs market. Furthermore, the fi ure includes both substandard and counterfeit drugs without breaking down the proportion of each.

[32] One study (Arcebido 2020) found that excursions happen for 1% to 5% of shipments. Another source (Barrowclough 2020) cited a study concluding that 25% of vaccines have reduced efficacy due o cold-chain failures and that 20% of all temperature sensitive pharmaceuticals have significant emperature excursions during transport. That same source estimated around 15% of temperature-sensitive pharmaceuticals were wasted.

We envision PharmaNet integrating with end-to-end condition-monitoring devices and services, where each unit has temperature tracking from the point of manufacturing to the point of consumption.[33] With the data from that end-to-end tracking, there are three main ways the proposed PharmaNet can help reduce excursion:

– *Chain-wide accountability and systemic improvements*—End-to-end monitoring provides more precise and irrefutable evidence about who is responsible when excursions occur. The unambiguous assignment of liability and associated fines p ovide strong motivators for all parties to improve their performance. On a more collaborative front, this type of rigorous monitoring allows systemic problems to be identified and jointly worked on. This may involve specific p ocess improvements, targeted training to particular personnel, improvements to equipment maintenance programs, upgrading of cooling systems, and so forth. The data may also be used during negotiations with logistics and distribution service providers to push for performance improvements as a condition of awarding more business.

– *Real-time alerts and actions*—Alerts generated in real time can be used to drive near-term corrective actions. For example, warehouse workers could be alerted when a shipment has been sitting too long in an uncooled location (e.g., a loading dock) and instructed to move it into cold storage. If the cooling unit on a truck or container starts failing, someone could be notified o take corrective action, such as exchanging vehicles or containers or having the cooling unit fi ed (if immediate repair is feasible). Such actions could prevent more severe excursions and the loss of those drugs.

– *Intelligent distribution and dispensing (stability-budget-based)*—The PharmaNet records cumulative temperature excursions for each end-consumable unit, recording the total time out of storage (TOS). This can be used to calculate the impact on each unit's stability budget,[34] thereby determining remaining shelf-life and any degradation to efficacy and sa ety. Based on this, more intelligent distribution and dispensing decisions can be made. A distribution center can send units that have less remaining stability budget to locations that are nearer, have better temperature controls or higher velocity consumption. Units with a larger remaining stability budget can be sent to locations that need that a bigger buffer due to lower consumption velocity or more challenging handling conditions. In this way, the total number of units discarded due to excursions is reduced. Similarly, doctors and pharmacists can be provided with precise remaining efficacy estimations to make more informed decisions for drugs that have been exposed to temperature excursions.

Temperature excursions

– *Key metrics:*
  - Excursion rate percentage (% of shipments)
  - Product cost of cold chain failure
  - Process cost of cold chain failure (e.g., diagnosis, returns and disposals, corrective actions).
– *Improvement mechanism:* Unambiguous assignment of liability and fines moti ates all parties to improve performance. Systemic problems are identified and ontinual improvements implemented include process improvements, training, and equipment improvements. Real-time alerts drive corrective actions, such as moving at-risk shipments into cold storage. Precise monitoring of remaining stability budgets enables more intelligent distribution decisions, increasing the portion of partially exposed drugs that are safely used and thereby reducing waste.
– *Typical improvement range:* 10% to 50% reduction in excursions. 10% to 50% reduction in product and process costs from cold chain lapses.

BioPharma Inc. hypothetical impact

- 80% of BioPharma's revenue comes from temperature-sensitive drugs
- 5% of shipments experience excursions, resulting in loss of product of $162M
- Logistics and other process costs for lost shipments = $32M
- 20% reduction in excursions using PharmaNet = savings of $39M
- Modest increase in customer satisfaction due to higher rate of usable shipments

By reducing excursions by 20%, BioPharma Inc. realizes savings of $39M, with equal increase in profit

[33] Ideally, each unit of end consumption has its own temperature tracking device that goes from the manufacturer to the dispenser. However, for smaller unit sizes, this can be quite costly. An alternative is to have a series of temperature trackers at the case, pallet, or conveyance level, with the PharmaNet providing an association between each of those and the individual units they contain. This way an end-to-end temperature history can be recorded by 'stitching together' the data from each segment of the journey for each end-consumption unit. This approach risks some blind spots during handoffs (such as sitting on a loading dock or tarmac) but is still much better than a fragmented view.

[34] Regulations require companies that bring a drug to market to maintain data on how long the drug lasts under different temperature conditions. This is known as the "stability budget," which determines how long a drug can stay at different temperatures and still be safely and efficacious y used. For more on this, see Stability Budget – The Key to Patient Safety in Cold Chain or Establishing Drug Stability Budget During Storage and Transit.

We estimate that taken together, these measures could enable PharmaNet to reduce excursions by 10% to 50% and reduce product and process costs by a similar amount. The size of the improvement opportunity will be at the higher end of this range for companies that have below average cold chain performance today and at the lower end of this range for those that already have above average cold chain performance.

Grey market diversion

Estimates of the volume of grey market[35] sales of drugs vary but are generally around €5B in the EU plus UK and $5B in the US.[36] Grey market sales harm profits or pharmaceutical manufacturers and revenues for authorized dealers who are playing by the rules. The beneficiaries a e the unauthorized distributors and patients who pay potentially lower prices. Research differs in what portion of the benefit oes to unauthorized distributors vs. patients, but regardless the consensus seems to be that the average amount of price arbitrage is around 20% to 40%. Assuming global grey market sales are in the neighborhood of $10B (i.e., about 1% of total global sales), that means 20% to 40% price arbitrage equates to an annual loss of $2B to $4B in profit or pharmaceutical manufacturers, or about 0.2% to 0.4% of revenue.

Trying to reduce grey market sales is a complex issue that technology alone cannot solve. It is very important to have strong contracts that obligate legitimate distributors not to source from or sell to unauthorized dealers, regular education and communications with distributors reminding them of these obligations (including requiring written confirmation that th y have read, understood, and agree to those conditions), and, in particular, rigorous monitoring and enforcement. Monitoring of grey market sales has become considerably more difficu t in the internet age of online ecommerce.

The proposed platform can help in several ways, fir t by facilitating regular communications and confirmation f agreements between pharma manufacturers and their authorized distributors. More importantly, the PharmaNet platform provides robust monitoring via end-to-end tracking of every chain-of-custody handoff. It becomes immediately apparent when a shipment of drugs is recorded as received by a distributor who in turn fails to record the sale of those drugs. With consistent recording of shipments received by pharmacies and healthcare providers, any shipments that did not flow through authorized channels can be spotted. Combined with consistent communications and enforcement, we estimate these capabilities could reduce grey market sales by 25% to 75%, thus returning $1B to $3B of profit back o pharmaceutical manufacturers and $2.5B to $7.5B of revenue back to legitimate authorized distributors.

Grey market diversion

- *Key metrics:*
  - Grey market sales, percentage of revenue
  - $ profit lo s due to grey market activities
- *Improvement mechanism:* The platform provides tools to communicate and periodically reaffirm ommitments from authorized distributors not to source from or sell to unauthorized dealers. It robustly monitors grey market sales by looking at the end-to-end chain of custody of shipments through multiple distributors to the dispensers.
- *Typical improvement range:* 25% to 75% reduction in grey market sales; 0.1% to 0.3% increase in profit or pharmaceutical manufacturers; 5% to 10% increase in revenue for authorized dealers in regions where grey market sales occur.

BioPharma Inc. hypothetical impact

- Currently 2% ($300M) of BioPharma's sales flow through grey market channels. These are sold at 20% lower profit or BioPharma then if sold through legitimate channels, resulting in a loss of net profit f $75M.
- Use of the PharmaNet platform, enabling robust communications and rigorous enforcement, results in a 50% reduction in grey market sales. Because of this, BioPharma Inc. realizes an increase in net profit f $37.5M.

Using PharmaNet, BioPharma Inc. reduces grey market sales from 2% of revenue to 1% of revenue, resulting in $37.5M increase in net profi .

[35] Grey market refers to the sale of goods through unauthorized channels or distributors. Though there are various reasons for grey market sales, it is often done to take advantage of price arbitrage opportunities. An unauthorized or unscrupulous dealer buys drugs in a market with lower authorized pricing limits and sells them at a profit in o a market with higher pricing limits.

[36] Estimates of €5B in the EU plus UK by (Chaudhry 2014) and $5B in the US by (Bandyopadhyay 2010).

Regulatory compliance and recalls

The PharmaNet platform can be used to comply with various regulatory requirements mandating consumption-unit-level serialization and end-to-end traceability or point-of-dispensing verification, such as DSCSA, EU's Falsified Medicines Di ective, and regulations from China, India, Turkey, Argentina, South Korea, Brazil, Saudi Arabia, the Russian Federation, and others.[37] The platform can generate, provision, commission, and aggregate serial numbers,[38] integrating with pharma packaging lines where the tracking of individual units begins. The application provides for scanning of shipments and units at the various process steps (e.g., pick, pack, and ship, receiving, put-away, repackaging, dispensing, etc.) at all stages throughout the end-to-end supply chain (manufacturing, distribution, dispensing). The value the platform brings for complying with pharmaceutical supply chain regulations can be measured in different ways, such as (in decreasing magnitude): 1) regulatory fines voided, 2) the cost of building a similar solution inhouse, or 3) the cost of buying a similar solution.[39] We use this last measure, the most conservative of these three, i.e., the cost of buying a set of solutions to provide similar functionality. We estimate that the annual subscription fee for similar functionality would cost smaller firms $50K o several hundred thousand dollars per year and larger firms $1M or mo e per year.

PharmaNet also enables recalls to be done more smoothly and rapidly, at a lower cost. End-to-end visibility of inventory saves labor in tracking down where the to-be-recalled product is and allows prompt notification o all parties holding the affected product. This includes notifying physicians and patients before the patient consumes the drugs, thereby preventing further harm. The platform also enables better coordination of reverse logistics and disposal. McKinsey estimates that end-to-end traceability can reduce recall costs by up to 0.3% of revenue.[40]

Regulatory compliance and recalls

– *Key metrics:*
  - Number of non-compliance events per year
  - $ of non-compliance fines per ear
  - Cost of compliance
  - Cost of recalls (percent of revenue)
– *Improvement mechanism:* The platform provides item-level serialization and end-unit-level end-to-end track and trace, thereby enabling compliance with drug supply chain regulations. It provides mechanisms for rapidly communicating and executing recalls, thereby lowering the cost and impact of recalls.
– *Typical improvement range:* When combined with effective processes, employee training, etc., compliance can be in the range of 99.9% to 99.999%. Recall costs can be reduced by up to 0.3% of revenue.

BioPharma Inc. hypothetical impact

- By implementing PharmaNet, BioPharma Inc. achieves a rate of 99.99+% compliance with DSCSA and other regulations. Implementing another solution to get similar results would cost them about $1.5M per year.
- Use of the PharmaNet platform reduces their cost of recalls by 0.1% of revenue or $15M.

Using PharmaNet, BioPharma Inc. achieves 99.99+% compliance, receiving $1.5M per year of value (i.e., the cost of implementing another similar solution). The cost of recalls, while varying from year to year, are reduced on average by $15M per year, with that amount going to the bottom line.$37.5M increase in net profit.

[37] For more, see The Coming Wave of Pharma Supply Chain Regulations

[38] Provisioning and commissioning associate each serial number with a specific individual physical unit of drug's package. Aggregation allows the system to track which individual units are packed into each uniquely identified inner and ou er pack, case, pallet, and shipping container. Aggregation management, combined with tamper evident seals, enables scan¬ning to be done at a case, pallet, or container level, rather than having to open them up and scan each individual unit.

[39] 1) The value of regulatory fines voided is potentially hundreds of millions of dollars for a large manufacturer. 2) The cost of building such a solution inhouse would be many tens of millions of dollars for a large manufacturer. Maintaining that solution over time would require ongoing spend of several million dollars per year.

[40] Of course, the actual savings will vary greatly between different companies and different time periods, depending on how many recalls are done within a given period and the size and extent of those recalls. According to (Blatha 2018), a report by McKinsey estimated a reduction in the cost of recalls by implementing track and trace of up to 0.3 percent of revenue for pharmaceutical manufacturers.

	Manufacturers	Distributors	3PLs and carriers	Retail pharmacies	Care providers	Patients
Patient adherence	High	Med.	Med.	Med.	High	High
VMI, auto-replenishment	Med.	High	Med.	Med.	Med.	Low
Shortages management	Med.	Med.	Low	Med.	High	High
Anti-counterfeiting	Med.	Med.	Low	Med.	High	High
Receiving, evaluated receipts	Med.	High	Low	Med.	Med.	Low
Expired drugs management	High	Low	Low	Med.	Med.	Med.
Cold chain	High	High	High	Med.	Med.	Med.
Grey market prevention	High	High	Low	Low	Low	Low
Recalls	Med.	Med.	Med.	Low	Med.	Med.
Regulatory compliance	Med.	Med.	Med.	Med.	Med.	Low
Inventory management	High	High	Med.	Med.	High	Low

Figure 5 – Potential value realization by pharmaceutical supply chain participants

Value for other pharmaceutical supply chain participants

A pharmaceutical chain-of-custody BSN provides value to other participants in the supply chain as well, not just the manufacturer. This is critical because achieving the full value of the BSN depends on adoption by various players up and down the chain. The leftmost column of Figure 5 lists each of the categories of value discussed in Value generated by an end-to-end chain-of-custody BSN. The top row of the table lists various players in the supply chain and below that shows the relative value each might expect to receive by joining the PharmaNet.[41]

Total value generated by a pharmaceutical chain-of-custody BSN

Significant otal value would be generated if PharmaNet were adopted widely across the pharmaceutical supply chain. Table 2 shows the total potential value if a platform like PharmaNet were adopted by 100% of the pharmaceutical supply chain.[42] Details on how each of these value estimates are derived can be found in *Appendix B: Value delivered by PharmaNet at 100% adoption*.

[41] Other upstream supply chain participants—such as API and inputs suppliers, CROs, and clinical trials services providers—were not included in this table because PharmaNet does not incorporate those functions or players in the supply chain. A different type of BSN (or an extension of the proposed PharmaNet functionality) could be created to serve clinical trials and inbound supply chain participants.

[42] In the real world, achieving complete 100% adoption is not realistic. The purpose of the 100% adoption calculation is to show the maximum achievable value (somewhat analogous to TAM). Adoption levels over 90% may be possible eventually.

Revenue	*Patient Adherence:*	Reduction in unfullfi led prescriptions	$ 120 B
	Expired Drugs Mgmnt.:	Reduction in return of expired drugs	$ 3 B
	Anti-counterfeiting:	Reduction in counterfeit drugs sold	$ 20 B
		Total Increased Revenue	**$ 143 B**
Pharmaceutical Supply Chain Cost Reductions/ Profit Increase	*Evaluated Receipts:*	Eliminating invoice issuing/processing	$ 2.4 B
	Shortages:	Reduction in pharmacy labor	$ 0.3 B
	Cold Chain:	Reduction in lost product (COGS saved)	$ 4.5 B
	Cold Chain:	Reduction in other excursion-related costs	$ 6.0 B
	Grey Market:	Profits ecovered by by reduction in grey market sales	$ 1.5 B
	Recalls:	Reduced cost of recalls	$ 1.0 B
		Total Pharma Supply Chain Cost Reduction/Increased Profit	**$ 15.7 B**
Healthcare Cost Reduction	*Patient Adherence:*	Increased adherence, reducing total healthcare costs	$ 45 B
	Shortages Mgmnt.:	Reduced spend on alternative drugs	$ 0.1 B
	Shortages Mgmnt.:	Reduction in shortage-caused healthcare costs	$ 20 B
		Total Healthcare Delivery Cost Reduction	**$ 66 B**
Compliance	*Regulatory Compliance:*	Value of regulatory compliance	$ 2 B
		Value of Regulatory Compliance	**$ 2 B**
Increased Productivity	*Patient Adherence:*	Improved productivity resulting from increased adherence for chronic disease treatments	$ 105 B
		Increased Productivity (Society-Wide)	**$ 105 B**
Working Capital	*Inventory management:*	Reduction in inventory while maintaining service levels	$ 22 B
		Working Capital Freed Up	**$ 22 B**

Table 2 – Total industry-wide value delivered by PharmaNet at 100% adoptions

Note Table 2 is not all inclusive and thereby may understate the overall benefit . We did not include, for example, benefits f om VMI or auto-replenishment. The table also only includes benefits for manufacturers, distributors, and dispensers—we did not include benefits o some of the other players in the supply chain, such as 3PL and logistics companies, insurers and PBMs, and packaging companies.

Value transferred to conveners of pharmaceutical BSNs
In a near-100% adoption scenario, we assume there will be at least two to fi e pharmaceutical BSNs covering the industry. A portion of the value generated can be captured by these conveners. The amount depends on the total addressable market (TAM) for this type of solution. Based on pricing for other industry solutions, we estimate that conveners could charge

in the neighborhood of 5% to 10% of the cost savings or profit increase or 0.2% to 2% of the revenue increase realized by the participants on the BSN.[43] Thereby, we estimate a TAM of $1B - $3B for the global pharmaceutical market for solutions similar to those described in this paper for the PharmaNet.[44]

Potential conveners of a pharmaceutical chain-of-custody BSN

There are several parties that might be a good fit or convening a chain-of-custody BSN for pharmaceutical supply chains. Some natural candidates include pharmaceutical software solution providers, distributors, logistics service providers, pharmaceutical packaging providers, and cold chain monitoring companies.

Pharmaceutical software solution providers
Pharmaceutical software solution providers are already in the business of providing solutions to pharma industry participants. Some already provide related functionality such as serialization, traceability, cold chain management, distribution, inventory management, anti-counterfeiting, and other components of the network we are envisioning. For some of them, it would be a natural evolution to extend their capabilities to the envisioned supply chain application network described above, thereby greatly expanding the value they provide and the pool of potential customers they serve. Solution providers would be seen as a neutral party (i.e., not a competitor within the pharmaceutical supply chain) and already have competencies to commercialize and operate software services.

Distributors
Distributors, in particular one of the big three,[45] would also be widely perceived as relatively neutral parties by manufacturers, retailers, logistics companies, and others in the chain (but not by each other, of course). They are right in the middle of the supply chain, already providing distribution, logistics, cold chain, and many of the services envisioned. While software is not their main business, many distributors have invested heavily in developing unique software capabilities to differentiate and add value to their service offerings, and in some cases earn additional revenue. Distributors are constantly looking for ways to differentiate themselves, beyond simply carrying inventory. Being the convener of PharmaNet would be highly differentiating, strategic, and potentially a generator of high-margin revenue for a distributor.

Logistics service providers
There are a number of 3PL firm [46] that specialize in serving the pharmaceutical industry. In the US. These firms mu t be registered with the FDA and pass inspections for temperature control, equipment control, proper chain-of-custody management, and security, among other things. As with distributors, 3PLs are always looking for ways to differentiate and sustain higher margins. Pharmaceutical 3PLs have already invested heavily in regulatory compliance and specialized services such as cold chain. In fact, the largest, fastest growing, and highest margin portion of their revenue is not from transportation or warehousing services, but rather from other specialized services such as packaging, customs and duty management, procurement services, and other value-added services. Pharma 3PLs already invest heavily in deploying software technology and, in some cases, custom-developing it. They would be viewed as a neutral third party by others in the chain. Providing a chain-of-custody BSN is a natural fit which ould help a 3PL differentiate and make their role in the network more strategic.[47]

Pharmaceutical packaging providers
Pharmaceutical packaging is a highly specialized, engineering-intensive business. Some packaging providers have been dabbling in "smart packaging," which includes embedding electronics such as RFID or NFC chips and even sensors in the package. Some pharma packaging companies have been experimenting with augmented reality technology, e-paper displays with buttons, as well as "connected smart packaging," platforms for end-user interaction, automated supply chain tracking of drugs, and other networked uses. Providing an end-to-end chain-of-custody BSN would be a natural evolution of this trend for the more advanced of these companies.[48]

[43] The percent of increased revenue that can be charged varies widely based on the profitability f the customers. High-margin users of the network (e.g., pharma manufacturers) should be willing and able to pay a higher percent of the revenue increases they realize by using the platform compared to the amount low profit margin customers (e.g., distributors) would be willing to pay.

[44] The $16B total profit inc ease for the supply chain at 100% adoption yields a range of $0.8B (5% of profit impact) o $1.6B (10% of profit impact). The $143B revenue increase yields a range of $290M (0.2%) to $2.9B (2%). Since pharmaceutical manufacturers are high margin, we use the high end of that range.

[45] "The big three"—McKesson, Cardinal Health, and AmerisourceBergen—together have over 90% (by some estimates 95 percent) market share for pharmaceuticals distribution in the US.

[46] The global biopharmaceutical 3PL market is estimated (by Grand View Research) to be about $100B in 2021, with over a third of that in the US.

[47] The pharma 3PL market is fragmented, which might make it challenging for any one player to gain the critical mass of participants necessary to create the network effect needed for a successful BSN. However, some of the players—such as FedEx, UPS, DHL, AmerisourceBergen, DB Schenker, Kuehne+Nagel, and others—have deep enough pockets to invest in attracting and growing a network of participants.

[48] One caveat: many packaging companies lack the depth of supply chain expertise required, which they would have to acquire to succeed. They may also lack the financial esources to launch a successful BSN.

Cold chain monitoring companies
Cold chain monitoring devices and services often are connected to software in the cloud, providing alerts and analytics. The companies providing these services have already developed supply chain-connected software systems, and they would be viewed as a neutral party. It might be a leap for most of them, as they tend to be smaller firm ,[49] but they would already have some of the needed expertise and strategic aspirations.

Potential for value-add services
Each of the potential conveners could use the PharmaNet to offer value-add services beyond those already described. With the proper permissions[50] and confidentialit -protecting safeguards, the aggregate anonymized data flowing through the network could provide tremendous value when mined by analytic engines and AI/ML-enabled algorithms. This might include price and performance benchmarking; insights for epidemiologists and clinicians based on visibility into what drugs are going where; trend spotting for 3PLs based on excursions and traffic; or mar et insights for manufacturers based on pricing and consumption. Countless other value-add services could be imagined. Once a network has reached a critical mass, the potential for value-add services built on top of the core BSN is vast.

Potential value for BSN conveners
The convener of a pharmaceutical BSN would realize significant benefit

- *Increased margins and revenue*—There is potential to build a billion-dollar-plus recurring revenue stream for a successful pharmaceutical BSN. This would be a high margin business, with profit ma gins typical of software solution sales. The margin impact is particularly attractive to low margin businesses, such as distributors and 3PLs.
- *More strategic relationships*—The services offered by the BSN—such as patient adherence, VMI and auto-replenishment, regulatory compliance, and other potential value-add services—would dramatically deepen and broaden the relationship between the convener and its customers, the participants on the BSN. These kinds of offerings create stickier, more resilient, deeper, and more strategic relationships.
- *Increased revenue for rest of business*—The BSN could be deeply integrated into the other services offered by the convener. Doing this would result in a major boost of revenue for the rest of its business as well.[51]

Taking an incremental approach

Think big, start small
As mentioned earlier in this paper, the BSN described here embodies a very ambitious vision. In a real-world setting, it would not be implemented all at once. Rather, the convener would likely select one area of functionality that was the best natural fit or the business and the needs of existing customers. A 3PL might choose to build on existing cold chain services to convene a cold-chain-focused BSN. The 3PL might get started by recruiting some key specialized cold chain carriers, cold storage providers, cold chain packaging companies, and cold chain-focused distributors to join its network. A pharma packaging company that already delivers anti-counterfeiting packaging features might convene an anti-counterfeiting BSN, recruiting one or more key distributors to get the network off the ground. A software company that already provides serialization capabilities might decide to convene a BSN for traceability regulation compliance.

Working with a company like IBM that offers deep consulting services and pre-built application logic, and already has experience convening many BSNs, enables companies to get started—even if they do not have a core competency in software development and commercialization. An experienced partner can help fi ure out the right business model, governance policies, where to start, and a roadmap for growth. A minimum viable network can be launched without having to bet the farm on a massive “do or die” project. Early successes can justify and fund further expansion.

As articulated in this paper, an enormous amount of potential value can be generated by a mature BSN with a critical mass of participation. In the past, building out this type of network functionality from scratch, and recruiting enough participation to achieve a network effect, has been prohibitively expensive and time consuming—out of the reach for most companies. Now, with the right partner and foundation, a BSN can be built in incremental steps and the enormous potential value unleashed.

[49] There are couple larger players in cold chain monitoring device and services, such as refrigerator manufacturer Carrier, who has over a million installed transportation refrigeration units. Most of the players are, however, quite a bit smaller.

[50] Participants could be incentivized to permit their data to be used *anonymously* for the purposes described here. For example, one potential incentive is granting access to exclusive or customized value-add services, such as benchmarking.

[51] This would have to be done carefully, so as not to be perceived as ‘lock in’ by customers, but rather perceived as the value-add of highly integrated complementary services (e.g., BSN plus logistics services plus distribution services).

Appendix A: IBM's blockchain offering for building a BSN

The IBM Blockchain Platform is a full-stack[52] managed Blockchain-as-a-Service offering, based on Hyperledger Fabric. While IBM has a very capable and widely used platform, in our opinion the three biggest differentiators, that make it especially well-suited for creating a BSN (Blockchain-based Supply Chain Application Network), are 1) unique, relevant consulting services, 2) extensive experience building and deploying BSNs at scale, and 3) pre-built application logic embodied in their Transparent Supply program:

1. *Consulting services*—On top of the IBM Blockchain Platform, IBM provides a set of consulting services to help with many of the challenges of building and sustaining a BSN, including:

   a. Technology design—specifica ly for thorny multi-enterprise technical design issues such as canonical data models, multi-enterprise MDM, multi-enterprise security, and design of multi-enterprise processes and applications
   b. Governance—help in crafting the rules of engagement for the BSN, i.e., how decisions are made and who has what authority, such as data ownership, control over code, transparency model, identity proofing policie , and so forth
   c. Business model design—help in fi uring out an effective monetization strategy, the best incentives to motivate widespread adoption among desired potential participants across the supply chain, and strategies for achieving critical mass and a sustainable business

2. *Experience building large BSNs*—IBM has built some of the world's largest existing blockchain-based supply chain networks, including TradeLens[53] (container tracking, >30M container shipments per year), Food Trust[54] (produce traceability, >40M transactions, 25K SKUs), we.trade (trade finan e, 16 banks, 15 countries, > €60M transactions), Responsible Sourcing Blockchain Network,[55] Marsh Proof-of-Insurance Blockchain, Atea Seafood Provenance Network, PharmaPortal, and Farmer Connect. While some are newer than others, certain of these blockchain networks (e.g., TradeLens and Food Trust) are among the most mature, highest volume BSN implementations worldwide to date.

3. *Pre-built application logic*—IBM Transparent Supply takes a big step further by packaging pre-built application logic for Trace (traceability, recall), Consumer (consumer-facing app), Insights (dashboards), and Documents (document management). Several major BSNs are already based on Transparent Supply, including Food Trust, Seafood Provenance Network, PharmaPortal, and Farmer Connect.

[52] The IBM Blockchain Platform is a permissioned blockchain where participating parties are known and authenticated, as is generally required for business transactions. It comes with a reference architecture comprised of software, services, development and management tools, and sample code to rapidly create, test, and manage blockchain networks. Software development tools include the Hyperledger Fabric SDK and Visual Studio Code extension. Operational tools include activation, policy editor, multiparty workflow simulation, network operations, and a business operations console.

[53] TradeLens has over 170 members, including 100+ port and terminal operators (covering over 600 ports and terminals), more than 20 ocean carriers and intermodal providers (serving over 60% of global shipping volume), and 10+ government authorities. The platform processes over 6M documents per year and captures >700M shipping events per year.

[54] Food Trust has over 280 members, including some of the largest grocers (e.g., Walmart, Carrefour, Albertsons), producers (e.g., Nestlé, Tyson Foods), and growers.

[55] Responsible Sourcing Blockchain Network, operated by RCS Global Group, provides mine-to-market traceability for minerals and metals. Members include Ford, VW, Volvo, and major mining companies such as Norilsk Nickel.

Appendix B: Value delivered by PharmaNet at 100% adoption

This section provides details on how we arrived at the estimated industry-wide value delivered by PharmaNet. It describes three scenarios with different penetration levels: 5%, 30%, and 100 $ The 100% scenario[56] would likely not be a single network, but rather two to four or fi e main interoperating BSNs.

5% adoption scenario (Single major supply chain)	**30% adoption scenario (Major market or region)**	**100% adoption (Universal adoption)**
Nearly complete participation across a single major supply chain. For example, a major manufacturer convinces most of its distributors and dispensers (retail pharmacies and healthcare providers) to join the network.	Wide participation across a major market or region,e.g., most US-based pharma manufacturers, distributors, and dispensers participate.	Nearly all players across the supply chain globally participate in the network.

	5% adoption	**30% adoption**	**100% adoption[64]**
Patient adherence—Studies show that 20% to 30% of prescriptions go unfulfi led (Viswanathan, et al. 2012). We estimate that use of the platform[57] would reduce unfulfi led prescriptions by 10% to 50%. For this value calculation, we assume a reduction in unfulfi led prescriptions from a current level of 25% down to a new reduced level of 17.5%.[58] At 100% adoption, that equates to an increase in revenue for dispensers of $120B. Manufacturers and distributors would see a somewhat smaller increase, as the dispensers' and distributors' margins would be subtracted out of that $120B total. About 50% of drugs for chronic diseases are not taken as prescribed (Marie T. Brown 2011). By coordinating caregivers and providing reminders, alerts, educational materials, and so forth directly to the patient, the platform can reduce non-adherence to 35% to 45%. If current rates of non-adherence were cut from 50% to 40%, it would save the global healthcare system about $45B per year and add $105B of productivity back into the economy.[59]	**$6B** revenue increase for manu-facturers[60] **$2.3B** healthcare savings **$5.2B** increased productivity	**$36B** revenue increase for manu-facturers[68] **$14B** healthcare savings **$31B** increased productivity	**$120B** revenue increase for manu-facturers[68] **$45B** healthcare savings **$105B** increased productivity

[56] In the real world, achieving absolutely 100% adoption is not realistic. Adoption levels of 90% or greater might be possible eventually. The purpose of the 100% adoption calculation is to show the maximum potential value.

[57] Along with implementing the programs and measures described in the *Patient Adherence* section above.

[58] This is a 30 percent reduction in unfulfi led prescriptions: i.e., 25 percent X 0.7 = 17.5 percent.

[59] Based on estimates of drug non-adherence adding $100B - $300B annually to U.S. healthcare costs (Viswanathan, et al. 2012), extrapolating to a global impact of $225B to $680B of added healthcare costs from non-compliance. Taking 10 percent of the middle point of this range, $455B, as the potential healthcare savings and estimating the economic cost of lost productivity averaging 2.3 times those added healthcare costs (Healthentic 2015).

[60] Distributors and dispensers (retail pharmacies and healthcare providers) would see an even greater increase, as their margins would be included on top of this number. Distributors margins average around 3.5 percent, retail pharmacy around 22 percent.

	5% adoption	30% adoption	100% adoption[64]
Receiving and evaluated receipts—We estimate there are about 120M invoices issued annually[61] across the global pharmaceutical supply chain. We estimate that transitioning to an evaluated receipts system would on average save about $20 per invoice in processing costs and reductions in dispute resolution, totaling $2.4B global savings and an equivalent boost to profit, primari y for retail pharmacies, healthcare providers, and distributors.	**$120M** process cost savings (increased profit	**$730M** process cost savings (increased profit	**$2.4B** process cost savings (increased profit
Shortages management—Shortages increase pharmacy labor costs by about $1B annually[62] due to time spent on activities such as gaining access to limited supply, finding orkaround strategies, and preparing for continued impacts. We estimate PharmaNet can reduce these costs by ~30% by providing better inventory visibility, better forecasting, a coordination mechanism between care providers, common policies, visibility into alternative treatments, and threat analysis to better understand the duration of the shortage.	**$15M** pharmacy labor savings	**$90M** pharmacy labor savings	**$300M** pharmacy labor savings
Shortages cause increased spend on alternative drugs of about $400M annually.[63] We estimate that PharmaNet can reduce those by ~25%.	**$5M** reduced spend on alternative drugs	**$30M** reduced spend on alternative drugs	**$100M** reduced spend on alternative drugs
There are significant other hea thcare costs not included in these numbers, such as loss of revenue due to delayed or cancelled procedures, staff overtime, and an increase in medication errors.[64] Furthermore, there are poorer outcomes, including additional deaths every year from shortages. While we could not find research quantifying the total cost of drug shortages for the healthcare system, one source indicated a cost of $13.7 billion had resulted to the US healthcare system due to a single shortage of norepinephrine. This is likely larger than most, but there are typically about 50 to 100 new drug shortages each year in the US. We extrapolate that the healthcare cost of all shortages in the US alone is in the many tens of billions, and perhaps near or over a hundred billion dollars. Globally the healthcare costs from drug shortages are likely $100B to $200B. We estimate that PharmaNet could mitigate the impact of those shortages on total healthcare costs by 5% to 20%.	**$0.5B - $1.0B+** reduction in total drug-shortage-caused healthcare costs.	**$3B - $5B+** reduction in total drug-shortage-caused healthcare costs.	**$10B - $20B+** reduction in total drug-shortage-caused healthcare costs.

[61] Our research indicates about 25M invoices are issued annually for drugs purchased by US-based retail pharmacies and healthcare providers. We estimate another 15M invoices are issued for drugs purchased by US distributors, thereby a total of about 40M invoices issued per year in the US drug supply chain. We estimate that the US accounts for about a third of global invoice volumes, thereby arriving at a fi ure of 120M invoices issued globally.

[62] Shortages cause about $350M/year in extra pharmacy costs in the US according to (Vizient 2019). We estimate the global number is about 3X that amount, as US drug volumes are about one-thirs of the global total (though spend is nearly half).

[63] Shortages cause about $200M in spend on higher priced substitutes in the US (Fox 2014). We estimate the global number is about 2X that amount as US drug spend is about ½ of the global total.

[64] About 6 percent of healthcare practitioners have experienced medication errors caused by drug shortages (Fox 2014).

	5% adoption	30% adoption	100% adoption[64]
Inventory management—We estimate there are about 250 days of inventory in the pharmaceutical supply chain, from manufacturing through dispensing.[65] This equals about $290B of inventory[66] in the global pharmaceutical supply chain (not including inventory at inputs suppliers). By our estimate, PharmaNet can reduce that by 5% to 10%, without negatively impacting service levels or shortages. For these calculations, we assume a 7.5% reduction in inventory, which is a reduction of about $22B of inventory across the industry, freeing up that amount of working capital.	**$1.1B** working capital freed up	**$6.5B** working capital freed up	**$22B** working capital freed up
Expired drugs management—Globally about $13B worth of drugs are returned to manufacturers due to expiration.[67] We estimate PharmaNet could reduce returns of expired drugs by 20% to 50% by providing highly granular, near-real-time visibility to identify where expirations are occurring and help diagnose why. Manufacturers, wholesalers, and dispensers can thereby reduce expirations through a variety of means, such as expiry alerts, better stock rotation, selectively holding back inventory at centralized DCs for end of season, better coordinated new product delivery, and other means. We estimate this could reduce expired drug returns by about $3B globally. In addition, about $2B worth of unused drugs are disposed by consumers.[68] We estimate PharmaNet could reduce that by about 30%, via reminders and interventions. This would benefit patients and the e vironment.	**$160M** reduction in expired drugs returned to manufacturers **$30M** fewer unused drugs	**$970M** reduction in expired drugs returned to manufacturers **$180M** fewer unused drugs	**$3.2B** reduction in expired drugs returned to manufacturers **$600M** fewer unused drugs
Anti-counterfeiting—We estimate slightly over 3% or $40B of drugs[69] sold worldwide are counterfeit. We estimate the PharmaNet platform could reduce counterfeits by 50%, by providing track and trace at every handoff in the chain of custody and by allowing any party at any stage (including the end consumer) to confirm that what th y are receiving is legitimate product. In contrast to counterfeit luxury items—which many people buy knowingly and thereby those purchases largely do not represent lost sales—almost all buyers of counterfeit drugs believe or hope what they are buying is genuine. Thereby, we expect the majority of reduction in counterfeit drug sales will translate into an increase in genuine drugs purchases.	**$1B fewer** counterfeit drugs sold	**$6B fewer** counterfeit drugs sold	**$20B fewer** counterfeit drugs sold

[65] This includes 180 days at manufacturers (including raw, WIP, and finished goods), 30 days in distribution, and 35 days in retail pharmacies and healthcare providers. The big three distributors average 29 days of inventory, but smaller distributors carry considerably more and a portion of inventory travels through multiple secondary distributors. Retail pharmacies average around 35 days of inventory. Numbers for healthcare providers were harder to find; e assume they are likely higher than retail pharmacy, but to be conservative, we are assuming 35 days also for healthcare providers.

[66] This includes $115B at manufacturers (180 days inventory @ 26 percent COGS), $86B at distributors (35 days inventory @ 96 percent COGS), and $90B at retail pharmacies and healthcare providers (35 days inventory @ 78 percent COGS).

[67] $13B of expired drugs (globally) are returned to manufacturers each year based on an estimated 1.5 percent of all drugs returned for credit (HDMA Returns Task Force 2009), with 72 percent of those due to expiration, and an estimated global pharma sales of $1,200B (average of several sources). Here, we assume the platform reduce returns by 25 percent = $3.2B/year.

[68] A report by the International Journal of Environmental Research and Public Health indicates that *"the value of unused medications generated by the population of US senior citizens alone is estimated to be over USD 1 bn per year"* (Alnahas, et al. 2020). Since the US represents approximately half of global drug consumption (by value), we arrive at $2B of unused drugs worldwide.

[69] Estimates of worldwide counterfeit drugs sold range from 2 percent to 10 percent and value estimates from $4B to $431B. Our re¬search indicates that global counterfeit drugs sales are around $40B or about 3 percent to 3½ percent of the global prescription and OTC pharmaceuticals market.

	5% adoption	30% adoption	100% adoption[64]
Cold chain—Pharma cold chain failures result in loss of about $15B of product annually and incur an additional $20B in related costs worldwide.[70] We expect PharmaNet to reduce cold chain failures and associated costs by 30% on average, through a combination of 1) *chain-wide accountability and systemic improvements* (end-to-end monitoring, unambiguous assignment of liability, systemic problem identification, p ocess improvements, targeted training, improved maintenance programs, upgraded cooling systems), 2) *real-time alerts and actions* (real-time alerts driving corrective actions), and 3) *intelligent distribution and dispensing* (continuous recalculation of each unit's stability budget based on end-to-end temperature history, driving more intelligent distribution and dispensing decisions).	**$225M** reduction in lost product **$300M** reduction in other excursion-related costs	**$1.3B** reduction in lost product **$1.8B** reduction in other excursion-related costs	**$4.5B** reduction in lost product **$6B** reduction in other excursion-related costs
Grey market prevention—Global grey market sales total around $10B (€5B in the EU plus UK and $5B in the US).[71] The average price arbitrage is around 30%, resulting in an annual loss of $3B in profit or pharmaceutical manufacturers. We estimate the proposed PharmaNet platform could reduce grey market sales by about 50%, replacing them with an equivalent number of legitimate sales. It does this by facilitating communications and confirmation f agreements between pharma manufacturers and authorized distributors and through robust monitoring of every chain-of-custody handoff.	**$75M** recovered profit or pharma manufacturers	**$450M** recovered profit or pharma manufacturers	**$1.5B** recovered profit or pharma manufacturers
Regulatory compliance—The proposed platform provides compliance with global regulations mandating unit-level serialization and end-to-end traceability, such as DSCSA and other regulations. The value of this compliance can be estimated by amount of fines voided or by how much it would cost to build or buy an equivalent solution. We use the most conservative of these, i.e., the cost to buy an equivalent solution. Our estimate for the 1,000 largest pharmaceutical companies (including manufacturers, distributors, and dispensers) is they would likely pay on average about $1M per year for a solution providing similar functionality. The next 10,000 companies would likely pay on average $100K per year. Adding up both groups brings a total market value of about $2B.	**$100M** value of regulatory compliance	**$600M** value of regulatory compliance	**$2B** value of regulatory compliance
Recalls—Pharmaceutical companies spend billions of dollars a year on recalls. McKinsey estimates that track and trace systems can reduce recall costs by up to $3.5B globally.[72] We estimate a more conservative fi ure of $1B cost reduction in global recall costs, enabled by the traceability that PharmaNet provides.	**$50M** reduced cost of recalls	**$300M** reduced cost of recalls	**$1B** reduced cost of recalls

Table 3 – Summary of value delivered by PharmaNet at 100% adoptions

[70] These losses are a combination of lost product, clinical trial loss and replacement costs, wasted logistics costs, and the costs of root-cause analysis (Cece 2020).

[71] Estimates of €5B in the EU plus UK by (Chaudhry 2014) and $5B in the US by (Bandyopadhyay 2010).

[72] According to (Blatha 2018), a report by McKinsey estimated a reduction of "up to 0.3 percent of revenue" in the cost of recalls by implementing track and trace.

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