Linking Pharma Manufacturing: CDMOs, Blockchain & Distributed Ledger Technologies (DLT)

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Executive Synopsis

The term blockchain is most often associated with cryptocurrencies such as Bitcoin, but the technology and its implications could have a more far-reaching impact on other industries including pharmaceutical manufacturing. Contract drug manufacturing organizations (CDMOs) and pharmaceutical developers could realize tangible benefits by implementing a variant of blockchain termed "Distributed Ledger Technology" (DLT). DLT promises to provide better transparency within the pharmaceutical supply chain, create cohesive hand-offs, increase traceability, and prevent fraud or counterfeiting. There are several ways to implement DLT within a pharma supply chain, including FDA mandate or guidance, leadership from a pharmaceutical company or consortium, or ecosystems that self-organize. Major challenges in executing a DLT include platform integrations, cost, governance, and accountability. To explore theoretical DLT applications, we illustrate using the drug product manufacturing fill and finish CDMO ecosystem of Argonaut Manufacturing Services.

How is blockchain different than DLT?

Simplified, a blockchain is a continuously growing chain of records that are cryptographically linked. Each record ("block") contains a link ("hash") to the previous block, a time stamp, and transaction data. Once data has been recorded in a blockchain, it is essentially impossible to alter undetected. If the data inside a block changes, so does its hash. To change one block, a hacker would have to change all blocks in the chain (this video[1] easily explains blockchain). Additionally, blockchains use a peer-to-peer network (each peer is a "node") to verify the integrity of the chain, using "consensus" algorithms as each new block is added. When consensus is reached, all nodes add the new block. The layering of hash, peer-to-peer networks, and consensus algorithms provide security in the chain and transaction integrity.

Blockchain can be defined as a decentralized digital record of transactions which records information permanently, with verification. This definition highlights three key features of blockchain. The first is *decentralization*. The data is stored in multiple nodes across a network of computers, as opposed to centralized storage where data is stored in a single location in the network. The advantage of decentralization is that there is no single point of failure. If one computer goes down, the others retain all the data. Furthermore, if one participant is a bad

actor, the data maintains its integrity in the other nodes. Finally, a central authority is not required for updating or verifying transaction data.

The second feature is *immutability*, which means that once the data is in the chain, it cannot be changed. Blockchains only allow the addition of new information; once the data is recorded in the chain it cannot be revised or deleted. Deep and detailed cryptography, which is beyond our scope here, enables this immutability.

The third key feature is *consensus*. Consensus protocols are a set of rules that specify how information will be verified before being written into the blockchain. There has been an explosion recently in the number and types of consensus mechanisms. For our purposes, it is sufficient to understand that a majority of participants in the blockchain network must agree that a transaction is accurate before it is entered into the chain.

Given this, how is blockchain different than DLT? A blockchain is simply a subset of distributed ledger technology. That is, all blockchains are distributed ledgers, but not all distributed ledger technologies are blockchains. When considering how this technology can impact pharmaceutical manufacturing, it is easiest to start without the constraints of blockchain. As an example, in pharmaceutical manufacturing the records will not be transactions, but are instead likely related to custody, manufacturing processes, final product testing and release, etc. Indeed, DLT and blockchain can store any type of information that the supply chain partners deem as valuable.

What is the potential of DLT in Pharma?

A 2018 article published by Accenture[2] postulates that DLT could be a $3 billion-dollar opportunity in the life sciences by 2025, and that "30% of life sciences organizations plan to utilize blockchain." The article advocates that pioneers in implementing blockchain will gain "competitive advantage and improved outcomes."

Consulting companies like Accenture will benefit from advising DLT services. Other beneficiaries will include DLT software organizations (such as Authentag and Stratis) and potentially shipping (including DHL) and supply logistics (for example, Chronicled) organizations. However, the impact will be most highly felt by those within the pharma manufacturing chain that must execute the DLT and work with it day-to-day. The pharma manufacturing chain exists as a business ecosystem (a network of organizations including suppliers, distributors, customers, competitors and government agencies). A DLT solution could impact subsets or potentially the whole ecosystem. To understand the practical implications of a DLT implementation, we look at factors that may positively or negatively impact a pharma manufacturing chain, using the existing Argonaut CMO/CDMO ecosystem[3] as an example.

How can DLT benefit and change CMO relationships?

DLT could be the data security, records, and data tracking/transfer answer that many pharmaceutical companies are looking for to solve the problem of compliance with the FDA's

Drug Security Supply Chain Act DSCSA. One enticing feature of DLT technology is that it can hold any format or type of information and ensure that drugs originate from the stated manufacturer.

Contract manufacturers would not only benefit from the potential regulatory compliance solutions of blockchain technology in drug manufacturing, but would also gain accurate tracking and delivery of the downstream product. Due to the peer-to-peer nature of DLT technology, manufacturing and lot/serial number data can be transferred securely and easily to different parties—from CMO (contract manufacturing organization) to pharma client. Each party, from manufacturing forward, has a single-entry point to the data that cannot be altered. This would not only streamline documentation of the supply chain but also secure the information digitally.

As an example, consider a pharmaceutical CMO/CDMO partner ecosystem that includes fill and finish services[4]. Here is how an ecosystem might work with DLT (figure 1):

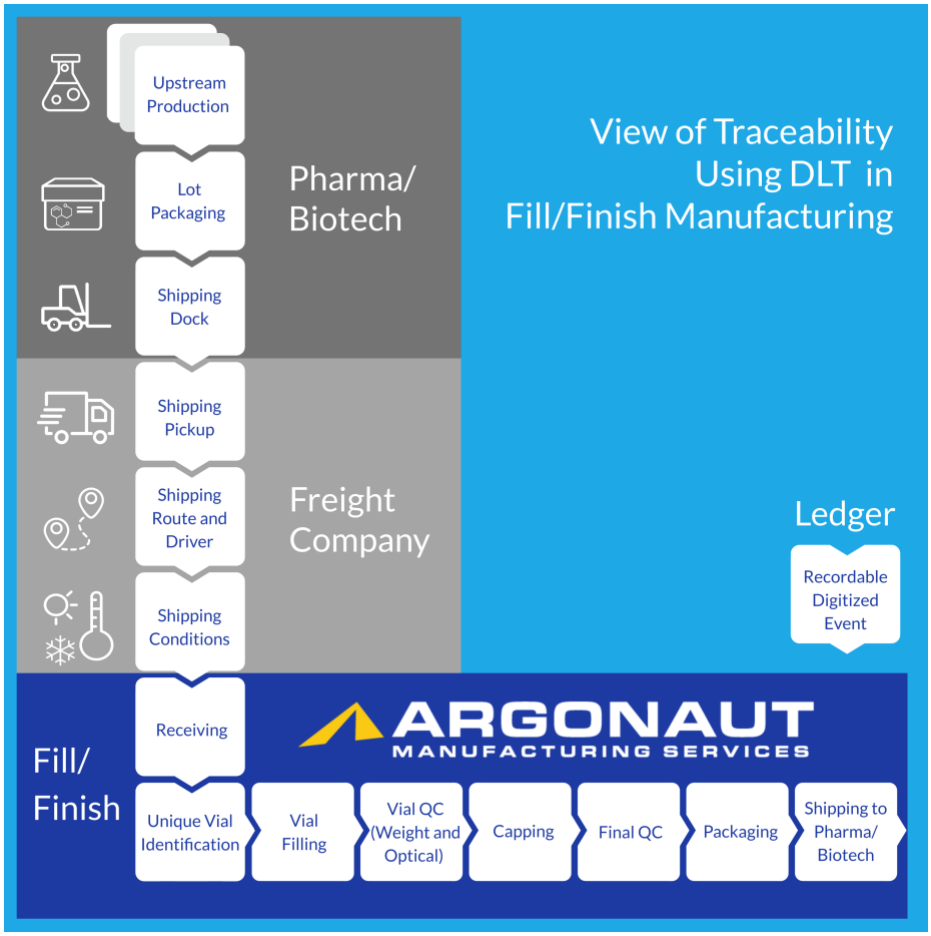

Figure 1 Example DLT traceability trail in pharmaceutical Fill/Finish manufacturing. Each event has a ledger that provides traceability.

The Active Pharmaceutical Ingredient (API) is received from a client, accompanied by packaging that includes a barcode linking the packaged components to DLT records from the shipping company. This information, in turn, is linked to the pharma shipping DLT

records, which is linked even further back to DLT records from the pharmaceutical manufacturing hub. As a node, the fill-finish CMO/CDMO verifies the product identity and registers the product. The registration creates a new block (record) which is consensus-checked for validity by other nodes within the system, including the pharma client. If consensus is agreed, the registration at the CMO/CDMO is added to the DLT record for the received product.

As the product proceeds through the CMO/CDMO's state of the art formulation, fill and finish process, new records are generated at steps that may include batch records, sampling protocols, and QC specifications. As each vial is filled, a new record is generated for each vial, creating complete visibility and traceability for the new components, including glass and stopper lots, fill records, vial position within the line, and operator. As the vial moves through post-filling, new DLT records for QC/QA are added. With all prior records, the pharmaceutical client has complete visibility and traceability in real time, including final shipping.

In our fill and finish example, the manufacturing ecosystem is linked with DLT, and there is potential for unprecedented granularity in the detail of pharma processes. The visibility of detail can streamline communications within the ecosystem and provide traceability down to the individual vial, rather than at the batch level, all while delivering a chain of custody that will be difficult to counterfeit.

Based on these benefits, DLT has an excellent upside for the entire pharma ecosystem. Next, we examine some factors that must be considered in delivering a DLT solution.

What would DLT implementation in a pharma manufacturing ecosystem look like?

Unlike cryptocurrency, the consensus mechanism in a pharma manufacturing system does not require a vast number of data miners to validate new transactions. However, it would require a validated peer-to-peer software solution[*]. Ideally, all ecosystem members would be invited participants in the DLT system. They would each operate nodes in the network and have permission to participate in achieving consensus and adding data to the DLT. The records would be private within the ecosystem, and the group maintains the integrity of the data.

There are at least three different ways a pharmaceutical manufacturing DLT system could be created: FDA-mandated or organized, pharmaceutical/or consortium-led, and/or self-organizing within the ecosystem.

1) FDA-Mandated/Organized: The FDA is in the exploratory phase regarding DLT, so it is unlikely they will mandate the technology in the near future. However, they recently announced a pilot program that "will inform the development of the enhanced electronic, interoperable track-and-trace system for industry set to go into effect in 2023 as part of the Drug Supply Chain Security Act.[5]" Under the Drug Supply Chain Security Act (DSCSA) all drugs

[*] Major players in this space include Oracle, Accenture SAP, and others

must be serialized or barcoded at the package level, but there is no centralized database to link with a prospective DLT. The FDA is also "considering using blockchain to track prescription medications[6]".

2) Pharmaceutical/Consortium: Several pharmaceutical companies are actively investigating and prototyping DLT. Novartis is working on a proof of concept with the "Innovative Medicine Initiative" (IMI) Blockchain Enabled Healthcare program[7]. The consortium is comprised of SME (small, medium entity) blockchain companies, universities, clinical labs, hospitals, patient representatives and others, with the aim of exploring use cases in counterfeit drug detection, supply chain, patient data, and clinical trials. Merck has partnered with SAP to develop a DLT-based app that assists in reducing counterfeit drugs. The "SAP Pharma Blockchain POC" enables distributors to verify returns. Closer in relevance to manufacturing, Novartis is also experimenting with blockchain and Internet of Things (IoT) technology to track drug temperatures during transit. Finally, MediLedger[8] is building a working group that includes Genentech, Pfizer, AmerisourceBergen, Gilead, and McKesson. Their blockchain-based solution aims to ensure security, traceability, and payment processing.

3) Self-organizing Within the Ecosystem: Closely aligned members within the pharmaceutical manufacturing workflow may find DLT advantageous even without an end-to-end solution. DLT solutions that provide transparency to supply chain issues such as smooth hand-offs, product quality, or cost reduction may be the most beneficial. As the problem that DLT will resolve is more defined in these cases, and there are fewer stakeholders needed for both trust and data definition, implementation may be faster and less expensive.

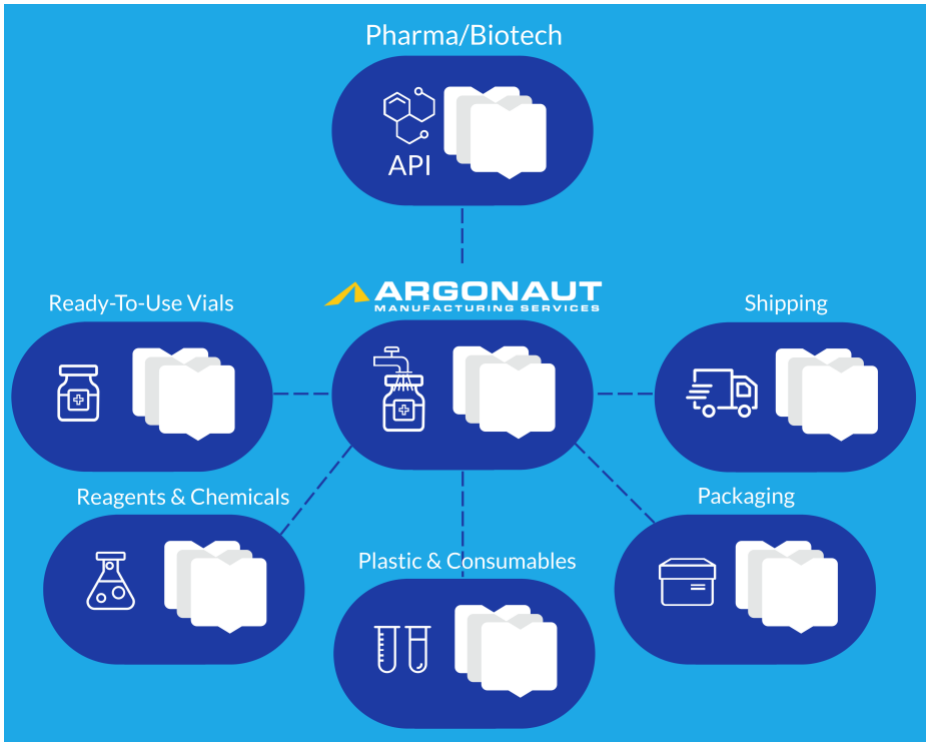

Figure 2 The DLT traceability trail encompasses the manufacturing ecosystem. Each ecosystem partner is permissioned to add to the distributed ledger.

Within the CMO/CDMO fill and finish example cited earlier, the overarching ecosystem could implement a DLT using just a handful of members (figure 2). This would include the pharmaceutical company, shipping logistic organization, CMO/CDMO, and key suppliers (such as those for glass vials, reagents, consumables, etc.). However, building a successful, simple DLT solution would be dependent on integration. Poor integration or members that create disruptions (such as slow-downs or inaccurate information) can create a ripple effect within the system. It is critical to keep in mind that even without incorporating a DLT solution, these existing disruptions are creating problems. DLT simply brings manufacturing issues to light as a side effect of traceability.

Potential risks and challenges

Since there are many possible DLT permutations, it is more valuable to approach at a broad view when considering implementation. Here are some high-level considerations:

Governance: The question of governance and data access will be one of the bigger hurdles in DLT supply chain implementation. Who is able to access what data and when is partially addressed by the DSCSA, but there are still many grey areas (figure 3). Supply chain members will likely request as much data visibility as possible, but deciding who gets this visibility, programming restriction/access, and validation measure control may prove challenging. The participants in the DLT will have to spend significant time working through these questions before even addressing the technology.

Blockchain and DSCSA Compatibility

Key Requirements	Applicability	Compatible?
Product identification	Unique product identifier can be required and contributed information validated as a side chain	✓
Product tracing	Allows manufacturers, distributors and dispensers to provide tracing information in shared ledger	✓
Product verification	Creates system and open solution to verify product identifier and other contributed information	✓
Detection and response	Allows public and private actors to report and detect drugs suspected as counterfeit, unapproved or dangerous	✓
Notification	Creates shared system to notify FDA and other stakeholders if an illegitimate drug is found	✓
Information requirement	Can create shared ledger of product and transaction information including verification of licensure information	✓

Figure 3 As blockchain technology is generally understood, it is well suited to meeting operational requirements of DSCSA compliance. Credit: Prof. Tim Mackey, UC San Diego

Costs: Building, deploying, and maintaining a supply chain DLT in the life sciences, biotech, and pharma industries is undoubtedly not an easy task. How the initiative gets funded will be an initial challenge to overcome, along with the costs of funding the DLT infrastructure at both an industry and company level. Costs incurred from implementing the platform are unknown, as partners within the chain will run across issues in repository access and

technicalities. There are several ways that these costs can be mitigated, however. These might include:

- Blockchain company membership dues
- Transaction fees
- Volume-based subscription models
- Data storage fees

Multi-Platform: One key challenge is on which platform the DLTs will run. It is likely companies will all have different platforms to keep their distributed ledger, but tying platforms together into a cohesive and seamless system may prove difficult. Interoperability of these platforms will be key to larger scale performance. In addition, a company may participate in multiple DLTs with their different supply chain networks, and it is likely that these DLTs will require separate management at the company level.

Data storage: The amount of data generated from global drug manufacturers down to the unit level will be staggering. Currently, many blockchain platforms charge a premium for storing data over a certain limit. Identifying an efficient and cost-effective solution to data storage in the supply chain DLT will be integral to its implementation.

Confidentiality: In order to maintain confidentiality of information in the DLT, data must be obfuscated. Additionally, un-obfuscation must be rendered impossible as data travels down the supply chain. There are several different ways to maintain confidentiality in the DLT, including:

- Data access limits and rules hard coded into the ledger
- Data encryption with approved members of DLT having access to decryption
- Certain data being obfuscated while other data is not, thereby limiting members to what data they can access

Skepticism and Lack of Trust: Settling on an effective and easily implementable mechanism to ensure confidentiality, while giving generous data access to approved members, might prove challenging. Yet, trust and security are the primary drivers to adopting DLT. Consider one example of blockchain: ending the trade in blood diamonds. Once the diamond is in the supply chain, the data associated with it may be secure, but those entering the data at the diamond mine may not be trustworthy. Indeed, the link between the digital information and the physical product is a critical challenge for DLT and blockchain.

Transparency to Outside Parties: It is unknown how third parties such as FDA regulators might choose to use the DLT information. However if DLT was implemented and validated it could streamline processes (for example, recalls). In one aspect, the auditing process may actually become easier as the records are better integrated. Without clarity on how regulators may engage with DLT records, there could be perceived risk in implementing a DLT solution.

Conclusion

Distributed Ledger Technology has tremendous potential to positively impact the pharmaceutical manufacturing chain. Benefits may include better transparency for the entire chain, improved chain of custody, faster ability to identify and remedy problems, improved hand-offs, and preventing counterfeit drugs. Pharmaceutical manufacturing DLTs may have data integrated or supplemented with IoT, including temperature recorders and fill and finish robotics. While there are numerous benefits to DLT, with such an early technology it is unclear how it will become established in the market. There are at least three potential routes including FDA mandates, pharmaceutical company leadership, and self-organizing pharmaceutical manufacturing ecosystems. Key actors, including CMO/CDMOs and other manufacturers, will play a strong role in implementing DLT's for pharmaceutical manufacturing. Some barriers to DLT in pharma manufacturing include governance, cost, and confidentiality.

As different pharmaceutical organizations test the DLT waters, the community continues to gain more experience and confidence in this new technology. If your organization is looking for a state-of-the-art CMO/CDMO for clinical vial or syringe fill and finish, consider Argonaut Manufacturing Services[4]. We have the latest technology solutions that reduce risks associated with particulate generation and human intervention. With In-line, non-destructive, weight tests and optical scans on each vial, we provide information useful for both today's quality systems and tomorrows.

Contact Us at (888) 834-8892 or info@argonautms.com

Summary:

- DLT (distributed ledger technology) is a linked record generation system that could profoundly change the pharmaceutical manufacturing system. It is distinctly different from cryptocurrency systems (such as Bitcoin).
- DLT within a pharmaceutical/CMO ecosystem could improve handoffs, transparency, and inhibit counterfeiting products.
- Within a pharmaceutical ecosystem implementation of a DLT would provide unparalleled, real-time visibility and traceability into the manufacturing process for pharmaceutical partners.
- There are three scenarios for implementation of DLT: a) FDA led or mandated, b) pharmaceutical/consortium led, and c) self-organizing
- Prior to implementation of a DLT system a series of questions should be addressed including those related to governance, cost, platform selection and data storage, building trust, and confidentiality.
- It is unknown how regulators may choose to use DLT information.

[1] https://www.youtube.com/watch?v=SSo_EIwHSd4
[2] https://www.accenture.com/t20180409T144103Z__w__/us-en/_acnmedia/PDF-71/Accenture_Blockchain_Innovations_Life_Sciences.pdf
[3] https://www.argonautms.com/ecosystem-partners/
[4] https://www.argonautms.com/drug-product-manufacturing/
[5] https://www.businessinsider.com/fda-considers-blockchain-tracking-prescription-medications-2019-2
[6] https://www.ledgerinsights.com/fda-dscsa-pharma-blockchain/
[7] https://www.ledgerinsights.com/eu-pharma-blockchain-health-innovation/
[8] https://www.mediledger.com/