Improving Reliability and Security of Global Cold Chain Logistics for Pharmaceutical Assets

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Overview

Global cold chains require multiple organizations to collaborate, which results in a heterogenous system of hardware, software and assets. Cold chains in the pharmaceutical industry are particularly challenging, owing to the stringent requirements associated with the movement of life-saving vaccines, cultures and medications. This article explores the current state of cold chain logistics for pharmaceuticals and identifies weaknesses in the lifecycle of a cold chain. The article also discusses how IoT can play an enabling role, and concludes with a summary of prevention and risk mitigation strategies.

Introduction

A cold chain is a variation of a supply chain, whereby the assets that must be moved have additional requirements of being kept refrigerated or in some other manner under control of environmental parameters, such as light and humidity. Exposure of the assets to heat or humidity, even briefly, can cause diminished efficacy or complete waste.

While it is logically simple to refrigerate or otherwise store an asset in an environmentally controlled container, great complexity and risk is introduced when assets must move between multiple parties through a holistic supply chain.

In this article, we will describe the current state of cold chain logistics following the use case of pharmaceuticals, where a known chain of custody and assurance of quality has enormous implications for the efficacy of vaccines and other medical assets.

Characteristics of Cold Chain Logistics

We can think of the cold chain as being the environmentally controlled lifecycle of a single good or asset and cold chain logistics as "a systemic project to ensure the quality and performance of goods in the production, storage, transportation, sales, and all aspects" of the product life cycle leading up to consumption of the product.[1] The single asset either has a continuous or broken cold chain. The overall machinations to store, handoff and transport the assets are the cold chain logistics. The importance of the following characteristics may vary across different types of assets, but they still must be considered at least in some manner to determine the efficacy of a cold chain logistics system.

Environmental Sensitivity

Every asset is sensitive to extreme environmental conditions. Excess heat spoils vaccines. Excess humidity fuels mold growth on fabrics. Excess light can destroy certain chemicals and films. There are many other examples of destructive environmental

[1] Wang, H., Lan, Y. and Kong, F. (2018). Research on Development Model and Strategy of Agricultural Products Cold Chain Logistics in Jilin Province. *IOP Conference Series: Materials Science and Engineering*, 452, p.022033.

factors such as vibration, gas composition, pressure and radiation. Most assets can be kept in standard atmospheric (i.e., ambient) conditions for a modest amount of time without suffering damage, but we cannot assume or rely on these kinds of gaps in the cold chain.

While we often need to control environmental parameters while manufacturing, storing and transporting assets to ensure the efficacy of the asset, it is unreasonable to spend far beyond the value of an asset. For food supply, general guidance is that logistics costs should not exceed 50% of the food cost.[2]

This guideline is harder to apply to pharmaceuticals, as the costs may be known but the societal value becomes difficult to quantify. An ineffective vaccine might lead to a human death. Even worse, a patient that we think is inoculated but truly is still at risk can inadvertently become an infection vector to other patients. To add complexity, different vaccines have varying sensitivities to heat and light.[3] There is not a single, perfect design for cold chain logistics to support all vaccines, so dynamic sensors and controls are critical.

Many Handlers

Many parties handle a vaccine during its lifecycle. First, the vaccine must be synthesized in a lab. Next, the vaccine is collected for transport. Then, transportation may occur over long distances using multiple modes of transportation such as by land, sea or air. Finally, local delivery brings the vaccine to the person that will receive the pharmaceutical.

Across these stages, there is ambiguity regarding who did what, for how long, and to what effect. The advent and adoption of cloud computing has made it easier for each handler to write logs to databases and keep all interested parties advised of the status of the cold chain.[4]

[2] Ji, G. and Guo, R. (2009). Research on the security of cold-chain logistics. *2009 6th International Conference on Service Systems and Service Management*.

[3] WHO. (2014). *Temperature Sensitivity of Vaccines*. [online] Available at: https://www.who.int/immunization/programmes_systems/supply_chain/resources/VaccineStability_EN.pdf [Accessed 9 Jan. 2019].

[4] Li, X., Wang, Y. and Chen, X. (2011). Cold chain logistics system based on cloud computing. *Concurrency and Computation: Practice and Experience*, 24(17), pp.2138-2150.

Stage Name	Handler Types	Enabling IoT Technologies
Manufacturing	Additive manufacturer Discrete manufacturer	Digitial twins Heavy edge compute Machine vision
Collecting	Land trucking Railway	LTE-M, 5G gateways Medium edge compute
International ports	Airplanes Ocean freighters	Satellite connectivity Heavy edge storage
Regional Hubs	Warehousing	Autonomous vehicles Track and trace
Freight	Land trucking Railway	LTE-M, 5G gateways Medium edge compute
City Hubs	Warehousing	Autonomous vehicles Track and trace
Local Delivery	Small trucks Cars	LTE devices

Figure 1: Stages of a Global Cold Chain

Evidence of Control

While sensors and IoT devices simplify the collection and logging of environmental parameters during the cold chain, there are still major concerns regarding evidence of control by a given party within the cold chain. Log files need to be immutable and unforgeable to be regarded as true evidence of control.

Blockchain and other distributed-ledger technologies have shown great promise in recent years to provide a distributed, immutable log shared by all parties participating in a cold chain logistics system.[5] Additionally, there needs to be a trust that participants acting within the system are properly authenticated and authorized. The Industrial Internet Consortium's "Industrial Internet Security Framework" [6] provides

[5] Plaga, S., Wiedermann, N., Anton, S., Tatschner, S., Schotten, H. and Newe, T. (2019). Securing future decentralised industrial IoT infrastructures: Challenges and free open source solutions. *Future Generation Computer Systems*, 93, pp.596-608.

[6] Industrial Internet Consortium. (2016). *Industrial Internet of Things Volume G4: Security Framework*. [online] Available at: https://www.iiconsortium.org/pdf/IIC_PUB_G4_V1.00_PB-3.pdf [Accessed 9 Jan. 2019].

guidance regarding the need to have a hardware root of trust built into the silicon used in the processing units of internet-connected devices.

To further complicate matters, it is nearly impossible to maintain an always-on internet connection throughout a global cold chain. Great advances have been made in cellular- and satellite-based communication networks but we must still accept a small amount of network downtown either during access-point handoffs or failovers.

Heterogenous Operating Conditions

There have been many attempts at creating frameworks to describe the utility of cold chain logistics systems, particularly for food. As there is typically a different handler for each stage of the cold chain (e.g., warehousing versus local delivery) and form factors between stages. This heterogeneity of inputs and outputs for different stages means we cannot assume a single container and connectivity type can be used to truly observe a cold chain from start to finish.

This fact of heterogenous operating conditions has led to optimization focused on a single stage of the cold chain.[7] While we should strive to improve what we can, it is a folly to overly optimize one stage (e.g., regional distribution centers) while neglecting another stage (e.g., local delivery).

RISKS ASSOCIATED WITH GLOBAL COLD CHAINS

A vaccine must make a long journey from fabrication in a lab to administration in the field. Along the way, there are many opportunities for both observed and unobserved damage.

Handoff

As damage can occur at any point in the cold chain, we cannot defer inspection solely toward the end of the chain. Typically there is some level of inspection at the handoff between stages in a cold chain. The inspections, for practicality, typically involve a sample of the assets instead of the entire population. For additive manufacturing (i.e., liquids and gases), a sample can be intrinsically trusted. For discrete manufacturing (i.e., solids), the likelihood of tampering and forgery increases drastically.

A palette with hundreds of assets will most likely be inspected by taking a sample from the outer layer of the palette. This ease of access reduces the complexity of the inspection but also increases the temptation for replacement, forgery, or other types of tampering. Vaccine vial monitors (VVMs) can be used to provide evidence of heat damage[8], but damaged vials can be hidden within larger lots midway through the cold chain. Also, VVMs cannot detect damage

[7] Accorsi, R., Cholette, S., Manzini, R. and Tufano, A. (2018). A hierarchical data architecture for sustainable food supply chain management and planning. *Journal of Cleaner Production*, 203, pp.1039-1054.

[8] Vaccination: rattling the supply chain. (2011). *Bulletin of the World Health Organization*, 89(5), pp.324-325.

from excessive freezing or vibration. In the end, the damaged vial will be found, but the responsible party will be unknown.

Authenticity

As the value of assets increases, the temptation for forgery and dilution increases. Within food supply logistics, saffron stands as a good example of risk and mitigation. Minimally invasive inspection methods were created that correlate spectroscopy and purity.[9] Additionally, the specific process for inspection was standardized as ISO 3632. Similar strategies should be adopted to create standardized inspection for common pharmaceutical asset types that require a cold chain.

Standards alone do not provide a guarantee of authenticity and purity. Tamper resistant IoT devices can be used for the inspection themselves, with the results written through machine-to-machine (M2M) communication to blockchain or other distributed database technology.

Root Cause for Damage

Each handoff between different parties within the cold chain creates a risk for false negatives, whereby one party takes over custody of the asset with the assumption that the asset is undamaged. These false negatives further delay the identification of the root cause. Data must be recorded continuously for us to have true confidence in the status of the cold chain.

As with inspection devices, tamper-resistant IoT devices can monitor environmental parameters of the cold chain and log data using unforgeable M2M communication. The ultimate goal for root-cause detection is to predict failure, repair equipment, improve processes and remediate the cold chain before assets have been damaged.[10]

Recall and Replacement

All participants in a supply chain agree to some manner of agreement regarding replacement of assets or repayment for damages. Identifying the responsible party often becomes a lengthy and messy legal exercise. For precaution, each party should be recalling any tainted or possibly tainted assets. Without clear identification of the root cause of damage, recalls will be broader and costlier than necessary and, undoubtedly, damaged vaccines will be administered to patients before the issue is identified.

IoT provides a great hope for faster identification of damaged pharmaceuticals, clear traceability to lot numbers, and hence much more focused and effective recalls. While vaccines are more generally administered, there are other medically related assets that are extremely costly to replace. An organ en route for a transplant

[9] Khilare, V., Tiknaik, A., Prakash, B., Ughade, B., Korhale, G., Nalage, D., Ahmed, N., Khedkar, C. and Khedkar, G. (2019). Multiple tests on saffron find new adulterant materials and reveal that Ist grade saffron is rare in the market. *Food Chemistry*, 272, pp.635-642.

[10] Anderson, R., Lloyd, J. and Newland, S. (2012). Software for national level vaccine cold chain management. *Proceedings of the Fifth International Conference on Information and Communication Technologies and Development - ICTD '12*.

can be replaced, but the cascading delays can cause irreversible damage to patients and severe loses in utilization of medical personnel, equipment and facilities.

Diminished or Unknown Efficacy

Assets managed via a cold chain may either be completely unusable after sustaining damage or the asset may have some alternate usefulness. For many vaccines, excessive heat reduces the efficacy but does not destroy them completely. The damaged vaccines can still be administered to patients within certain age ranges and yield expected efficacy for those patients. However, the same damaged vaccines would not be effective if administered to patients outside of this age range.

The ability of IoT to provide more granular monitoring provides more resilience to the cold chain by identifying the lots or individual assets that have been minorly damaged yet can still continue within the cold chain to deliver expected results without compromising other assets or patients.

Energy Consumption

The energy costs for maintaining a cold chain can be significant. [11] Without detailed sensing and asset tracking, the participants in the cold chain will either have to use far more energy than is necessary, or they will be taking on unacceptable risk for spoilage. The survival of assets is paramount, but we must also strive for reducing energy usage whenever possible to meet green standards needed to be ethical participants in sustainable supply chains.

Suggested Improvements to Global Cold Chains

While the maintenance of a global cold chain is challenging, new technologies afford ways to improve the reliability and immediacy of monitoring goods. Additionally, distributed ledgers allow for increased trust by all participants in the cold chain. Combining immediacy and trustworthiness opens new possibilities for how we can improve the reliability of cold chains while reducing risks and costs.

Trusted Handoff Spaces

Varied lot sizes, transport modalities and regionalized data laws makes it unlikely that we will ever be able to have a single, standard way to move goods. As such, there will be a continued need to hand off a shipment from one party to another. During this handoff, we should provide redundant environmental isolation, such as a refrigerated crate being transferred within a refrigerated loading dock. These double-sealed locations can be designated as trusted places to take actions that would otherwise be deemed a breaking of the cold chain. For example, a tamper-resistant seal on a container owned by one party might need to be broken to shift goods to another container. Additional documentation and

[11] Chen, S. and Lan, H. (2016). The cold chain logistics enterprise's green level evaluation. *2016 International Conference on Logistics, Informatics and Service Sciences (LISS)*.

logging will need to be done in these trusted spaces.

Real-Time Tamper Detection

The majority of time in a good's lifecycle is spent between trusted spaces, notably during transportation. During this time, the custodian of the goods should provide real-time monitoring of the good for both environmental parameters but also for tamper attempts. This can be done through a combination of pressure, light and vibration. Sensor readings should be logged frequently and to a distributed ledger to prevent retroactive manipulation of data.

Distributed Ledger for Trustworthiness

The great hope of blockchains and distributed ledger technologies is to provide an immutable log of transactions. These transactions do not need to be financial but instead can be sensor readings proving the maintainance of the cold chain. Depending on the privacy implications of the goods, it may be necessary to use a private distributed ledger versus a public distributed ledger. The benefits of private distributed ledgers are beyond the scope of this article, but in short, there are energy/computation benefits of using private distributed ledgers for logistics when all parties within the cold chain are assumed to be known to each other.

CONCLUSIONS

IoT provides new ways by which we can monitor pharmaceutical assets such as vaccines in an unbroken cold chain from creation to administration. Further, new capabilities in data acquisition and edge-computing analytics capabilities now allow us to predict failures and remediate equipment before assets have been damaged.

Heterogeneous operating environments will continue to pose challenges, but advances in global cellular connectivity and distributed ledger technologies provide logical solutions to having real-time, tamper-proof asset monitoring for pharmaceuticals moving through cold chain logistics systems.

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