Meeting the FDA's Initiative for Protecting

the US Drug Supply†

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The complexity of the United States health care system is increasing rapidly. Demographic changes, along with a host of new drugs, are causing greater volumes of raw materials and finished products to move through the pharmaceutical supply chain. In many ways, the pharmaceutical supply chain is beginning to resemble the distribution of consumer goods (Cottrill 2001). However, several important differences remain.

The fundamental goal of the medical industry is patient care and safety. To achieve these goals for the public good, the Food and Drug Administration (FDA) and individual States regulate the industry through laws and administrative orders designed to protect the integrity of drugs throughout the pharmaceutical supply chain. Specifically, the Prescription Drug Marketing Act (PDMA) of 1988 calls for transactional history to follow individual packages of drugs throughout the supply chain from manufacturing through wholesalers and finally to retail outlets such as pharmacies and hospitals.

The FDA uses the term "pedigree" to denote the requirement for documentation of transactional history.   The pedigree requirement, legislated as part of the PDMA has is on hold because of practical limits in terms of implementation.   Determining a pedigree for all the drugs in circulation would require millions of pages of information to document the flow of drugs from manufacture to consumption (Mitchell 1998).

With a recent renewed threat of counterfeit medications entering the US pharmaceutical supply chain, greater interest exists in achieving full implementation of pedigree laws first outlined in PDMA.   While the number of counterfeit cases in the US remains below that of developing countries such as India and China, an increase has occurred from an average of five cases per year prior to 2000, to over 20 cases per year currently (FDA 2004).   By some estimates, counterfeit "can make up 2% to 7% of all drugs in the United States and as much as 80% in some Third World countries (Whiting 2004)."

Since the US pharmaceutical market is vulnerable to fake drugs, manufacturers have introduced a variety of measures, such as color shifting ink, holograms, fingerprints, and taggants, in an attempt to thwart counterfeiters.   All of these technologies share the common strategy of

placing some indicator on the package, or the drug itself, as a means of verifying authenticity.

However, it appears by using various computer and packaging technologies, counterfeiters have the ability to quickly imitate these measures and infiltrate counterfeit drugs into the legitimate drug distribution chain. By some accounts, counterfeit and theft combined cost the pharmaceutical industry $30 billion per year (Malykhina 2004).

In February 2004, the FDA released a report on the future role of RFID technology in the prevention of counterfeit medicines (Mathews 2004). The report outlined renewed focus on track, trace, and authentication of medicines and established a deadline of January 2007 for implementation of RFID based technologies to accomplish these tasks. Previously, Mark B. McClellan, FDA Commissioner had stated the goal of "…build[ing] a 21st century system that can better protect consumers against this emerging public health threat (Greengard 2003)."

The February 2004 report goes on to state "use of mass serialization to uniquely identify all drug products intended for use in the United States is the single most powerful tool available to secure the U. S. drug supply."

RFID and mass serialization are fundamental in creating a pedigree for drugs on a wide-scale basis. Implicit in the generation of a pedigree is the administrative requirement to do track and trace. **Tracking** involves knowing the physical location of a particular drug within the supply chain at all times. **Tracing** is the ability to know the historical locations, the time spent at each location, record of ownership, packaging configurations and environmental storage conditions for a particular drug.

Track and trace forms the foundation for improved patient safety by giving manufacturers, distributors and pharmacies a systemic method to detect and control counterfeiting, drug diversions, and mishandling. These are important aspects of supply chain security. Unfortunately, the current system for the documentation and organization of data is cumbersome because of a reliance on manual procedures and storage of information on

paper. As a practical result, track and trace takes place only in an emergency such as a drug recall.

Auto-ID technology offers the prospect for an integrated solution to the track and trace problem (Dinning and Schuster 2003).   The open standards feature of the technology aids in the implementation of a supply chain wide application. In addition, Auto-ID sets the foundation for a number of other applications within the health care industry (Brock 2002).

As the pharmaceutical industry faces a future that will include more worldwide outsourcing of manufacturing, there will be an even greater need to secure and maintain control of the supply chain to ensure that no counterfeit drugs enter the US.   In achieving this goal, it is important to understand the strengths and drawbacks of various identification technologies.

RFID VS AUTO-ID TECHNOLOGY

A great deal of confusion exists concerning the meaning of two terms, radio frequency identification (RFID) and Auto-ID. While RFID has been in

existence for more than 50 years, Auto-ID represents a new technological development (Sarma et al. 2000). Though both technologies share commonalities, several important differences exist (Schuster et al. 2004).

The term Radio frequency identification (RFID) generally refers to a class of technologies consisting of tags and readers or interrogators.   Tags are attached to objects and relay identity information to readers through radio frequency electromagnetic fields and waves.   Many different types of tags exist operating at different frequencies with different modes of coupling, communication, and power sources (Scharfeld 2001).   The origins of the technology trace to World War II where ground based radar began identifying friendly aircraft equipped with a transponder.   The first situations where business used RFID to improve operations did not occur until the 1970s. Early applications included tagging of animals and rail cars.   TABLE 1 gives a brief timeline of RFID.

TABLE 1

A Brief History of Radio Frequency Identification

1940s	1960s	1980s	1990s	Today
●WWII Friend or Foe	●EAS	●Railcar Tagging	●Security Access & Control	●Low cost tags
		●Animal Tracking	●Highway Toll Passes	●IT Infrastructure
			●Vehicle immobilization systems	

Through the 1980s and 1990s, RFID experienced additional growth. Some of the more popular applications included security and access control, vehicle immobilization systems, and highway toll passes.   Along with this growth came a proliferation of different technological formats leading to fragmentation of not only the technology, but also the markets.   The technology found success in "closed systems" where tags would be applied to a consistent set of objects and be read in well-known and controlled conditions.

Though RFID has offered some highly innovative applications, the technology has never achieved mass use in supply chains because the cost of the electronic tags remained relatively expensive and open standards did not exist.   This all changed during the late 1990s. The MIT Auto-ID Center and its community of sponsors formed to develop a system and standards driven first by the needs of users.   A user driven process coupled with specialized technology design and development of high-speed, high volume manufacturing techniques for tags provided useful technology standards, high demand, and a path towards low cost.   Projections show that the new generation of tags will reach a price point that allows individual tagging of

cases and pallets.   At some time in the future, the price might be low enough to tag individual consumer goods.

Given the scale of supply chains that include billions of items, a need exists for a comprehensive information technology infrastructure to manage the large amount of data potentially available from linking objects to the Internet.   With such an infrastructure, the practical possibility exists of ERP systems having continuous communication with objects located anywhere within a supply chain.   This *Internet of things* will create unprecedented interconnectivity, and have an important impact on the ERP systems of the future.

The infrastructure needed to manage the Internet of things is Auto-ID technology, an intricate yet robust system that utilizes RFID.   Release 1.0 of Auto-ID technology is managed by EPCglobal, a wholly owned subsidiary of GS1. GS1 is a result of the merger between the Uniform Code Council (UCC) and EAN International. The UCC was responsible for implementing standards for bar codes beginning in the 1970s. This has been one of the most successful efforts in establishing universal standards during the entire recorded history of

commerce. Arguably, bar codes top the list for innovative technologies developed during the 20th century.

An important feature of Auto-ID technology includes open standards and protocols for tags and readers, IT infrastructure interfaces, and data codes and formats. This means that all components, whether hardware or software, can interoperate, regardless of vendor.   DIAGRAM 1 provides a simplified schematic of Auto-ID Technology.

DIAGRAM 1
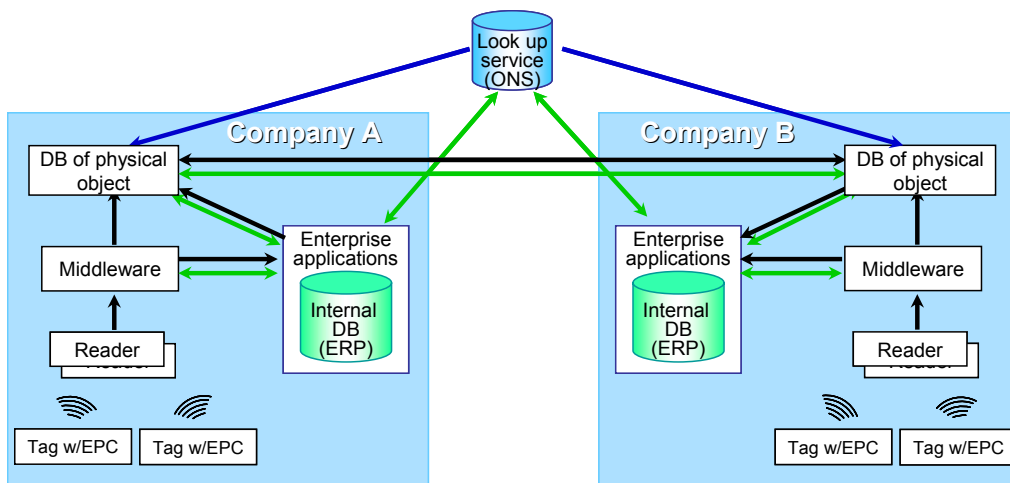
With this structure, identification of individual units becomes possible though the electronic product code (EPC), which has the capability for unique identification of trillions of items.   Unique identification on this scale results in useful information for track and trace (Koh et al. 2003a; Schuster and Koh 2004), the authentication of objects located anywhere in a supply chain (Koh et al. 2003b), and the management of versions of the same item code (Engels et al. 2004).

THE ADVANTAGES OF AUTO-ID TECHNOLOGY

Bar codes relay a small amount of information that identifies the manufacturer and links to a description of the object.   Non-profit standards groups such as GS1 administer the numbering system used for the bar code ensuring a unique identification without duplication by other firms.   All bar codes have limitations including:

- The need for a direct line of sight from the scanner to the bar code,

- The ability to read only one code at a time,

- The need for human intervention to capture data or to orient packages in the case of overhead bar code readers.

- Inflexibility in supporting greater amounts of stored data and enhanced functionality (i.e. sensors).

There is always a chance the bar code will be missed or in other cases, read twice.   As well, bar codes can be damaged or compromised in a way that makes them impossible to read.   All of these factors contribute negatively to the capture of data using bar codes.   Combined with the lack of unique identification, bar codes represent a mature technology that has reached the peak of operational usefulness.

IMPLEMENTATION ISSUES

The initial research and development for Auto-ID technology occurred in the consumer goods industry.   Early on, an influential group of consumer goods companies, including Proctor & Gamble and Unilever, and retailers such as Wal-Mart and Target, recognized the potential of Auto-ID.   In many ways, the technology represented the next generation of bar code.   Since consensus agreement existed within the consumer goods industry that bar codes were hugely successful since implementation during the 1970's, much enthusiasm existed for full development of Auto-ID.

While a number of pilot tests proved commercial viability within the consumer goods industry, the process of full-scale deployment is just now beginning.   With no proven benchmarks, it is not clear whether the pharmaceutical industry will take a similar implementation path.

For example, tag readability issues might be a source of significant divergence.   In the case of the consumer good industry, methods exist to compensate for the current lack of 100% read rates.   These same methods are probably not effective in the pharmaceutical industry where 100% read rates are an important element of automatically generating an electronic pedigree for every step of the supply chain.

Overall, the tag read rate is perhaps one of the most significant issues

facing the pharmaceutical industry as the deadline approaches for implementing an electronic based system to generate a pedigree. The next section provides a balanced appraisal of this issue.

Factors that Influence Read Reliability

RFID adds an additional layer of intricacy in obtaining an accurate read as compared to bar codes. Because bar coding is a mature technology with fifty years of testing and development, conditions necessary for successful production and use are well understood. Further, because bar codes depend on optical means for a successful read, the technology is direct and understandable. As long as the correct conditions exist, read reliability should be high.

Yet with RFID, tags are coupled to readers via radio-frequency fields and waves that are invisible to the human eye. As a result, read performance can seem highly variable and sometimes difficult to predict because it is hard to visualize the properties of electromagnetic fields. In addition, environmental factors play a much larger role in negatively affecting performance as compared to bar codes (Scharfeld 2003). Materials surrounding or blocking

tags, such as liquids and metals, can absorb and reflect the radio frequency energy.   Humidity, not a factor in bar code reading, can significantly reduce the read range for RFID tags.   A final complicating factor is that the manufacturing process for tags has still not achieved critical mass.   In some cases, manufacturing imperfections lead to poor read reliability.   This type of failure is independent of environmental factors influencing electromagnetic fields, and causes complexity in achieving high reliability.

Reliable and accurate reading of RFID tags is generally not a problem for a specific process if thorough testing and debugging is possible as part of the installation.   However, in open system applications such as tracking an object throughout the supply chain, neither the applicator of a tag, nor the integrator of a reader installation have direct control over a single implementation.   The old of model of deploying RFID is no longer applicable (Scharfeld 2003).   Current research and development efforts are focusing on standardization and testing to improve tag and reader designs, thus overcoming the effect of environmental factors in achieving 100% read reliability.

During the path toward 100% read reliability, many companies are

considering adopting an "inferred read" approach. By associating all items

within a case to that case, or all cases on a pallet to that pallet, a successful

read of some fraction of the aggregation can be used to represent a successful

read of all objects in the aggregation. For example, if a full pallet contains 60

cases (each tagged), then a successful read of only one of the EPC tags implies

that a complete pallet has been read. The Auto-ID approach, where

information is held on the network rather than in tags, is a great advantage in

facilitating inferred reads. However, the inferred reads approach assumes

that the aggregation is always intact i.e. all items are in a case or all cases are

on a pallet. This is a disadvantage when data is needed for such things as a

drug pedigree where the EPC code for each package must be linked to previous

shipments. If a high reliability read of RFID tags placed on each package of

drugs is not possible, the tracing information must be entered manually. With

the large volume of drugs moving through the supply chain, even partial

manual entry of information needed for the pedigree might be overwhelming.

Besides tag readability, a number of other issues exist that must be

researched before commercial application. These include:

Choice of radio frequency Standard – An important variable in achieving successful reads for tags is the frequency employed.   Specific frequencies work better in certain situations such as scanning tags placed on objects that are metal or contain liquids.   It is possible that the final implementation of Auto-ID in the pharmaceutical industry will mean different tags frequencies all working together.   For example, one frequency could be used tags placed on individual packages and a different frequency for tags places on cases and pallets.   To understand what works best, the pharmaceutical industry will need to go through a process of trial and error in testing tags of different frequencies before deciding the best mix of frequencies to use.   An important part of this process is full scientific and engineering knowledge of the properties associated with electromagnetic fields and RFID.

Product stability - Before large-scale application of RFID can take place in the pharmaceutical supply chain, testing must occur concerning the impact of electromagnetic fields on the stability of drugs. Increasingly, pharmaceutical products are becoming highly bioengineered molecules that are inherently unstable in nature.   Though there is no direct evidence that the levels of electromagnetic energy associated with RFID are high enough to cause product quality problems, testing must take place to provide empirical evidence for conclusive proof.

Electromagnetic compatibility – Hospitals and medical clinics are filled with complex electronic equipment.   Specific frequencies of radio waves that are associated with RFID tags might negatively affect the operation of life saving medical equipment.   Potential interference must be completely understood before full-scale implementation can take place.

The Code Structure of the EPC System – Identifying an individual item within the supply chain by using a mass serialized identifier is the corner stone of the EPC system. There are two approaches to code structure: 1) use the EPC as a substitute for existing codes, such as the NDC, or 2) create a new structure by nesting previous codes, such as the NDC, within the EPC.   The decision on which approach to adopt has worldwide implications because each country has a different code structure for the current identification of drugs. With outsourcing of manufacturing occurring on a worldwide basis, this will become an important issue for consensus.

ONS constraint - One of the important design characteristics of the EPC system is the storage of a small amount of data on the tag, (the EPC, a 96 bit serial number).   Storage of relevant information about the object (drug) resides on servers that can be accessed through the Internet.   The mechanism to link the EPC to a server location is the Object Naming Service (ONS).   One fundamental problem of the current release of ONS is that it does not specify the linking mechanism at an individual item level.   This means that

a drug can be traced to an individual manufacturer, however, no link through the EPC exists to specific information about the drug located on the manufacturers' servers.   This offers significant drawbacks in authentication of specific drugs and the generation of a pedigree that accounts for all drugs within a lot.

Privacy issues – With the potential of linking specific drugs to an individual through a large-scale system, maintaining privacy is a significant issue.   Maintaining privacy is perhaps the most important issue for further research.   The direction of this research will probably move toward various encryption technologies to cipher the link between a specific drug and an individual.

Redundancy – A final issue worth considering involves the need to build a redundant system for securing the pharmaceutical supply chain.   The dispensing of drugs is sometimes a life or death situation.   If verification of the authenticity of a drug is not possible because of system failure, then lives could be lost.   Before full implementation of Auto-ID technology can take place in the pharmaceutical industry, significant research must take place to ensure system reliability never becomes a factor in slowing the administration of drugs.

CONCLUSION

While application of Auto-ID technology to combat counterfeit is compelling, several factors offer complexities that must be overcome before full implementation can take place. The Auto-ID approach assumes that all drug manufacturers, carriers, wholesalers and pharmacies have the necessary hardware and computing ability to read and process EPC information. It is unrealistic to believe that this capability will occur immediately. However, the underlying structure to the pharmaceutical industry, which is relatively concentrated, could make the job of implementing an industry wide Auto-ID solution to detect and control counterfeit easier because there are fewer major players.

The Auto-ID approach will have to be fine-tuned in terms of information synchronization among many different supply chain partners to ensure a high level of reliability for pedigree and drug verification information. If a single supply chain partner does not properly handle information, pedigrees might show gaps that would raise counterfeit questions. The Auto-ID approach assumes different entities within the pharmaceutical supply chain can achieve a common level of cooperation in supporting the information infrastructure.

Besides proposed applications in improving track and trace, and drug

verification, Auto-ID infrastructure also serves as the foundation for future

applications of importance to the health care industry.   For example, the

Human Genome Project creates greater opportunities for engineering drugs to

treat small groups of individuals that suffer from specific illnesses (Philipkoski

2003). These "designer drugs" will be manufactured in small lot sizes on a

make to order basis. In this environment, logistics and coordination takes a

new form as thousands of biotechnology drugs flood the pharmaceutical

supply chain. Delivery of these new drugs to the right group of people presents

a challenge that the current logistical system cannot handle effectively.

Auto-ID lays the foundation for the management of this not-to-distant

complexity and provides the framework for a Safer and Securer Supply Chain.

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