RFID Solutions and the California Pedigree Mandate
Combating Drug Counterfeiters and Ensuring Patient Safety

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RFID in Manufacturing and Supply Chain
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Counterfeit Drugs: Intro

In 2003, the FDA announced a recall of 200,000 bottles of Lipitor (a popular cholesterol lowering drug) that was discovered to be counterfeit. 110,000 bottles of Epogen and Procit, drugs to boost red blood cell production for cancer and AIDS patients were also found to be fake [1]. In that same year, the WHO (World Health Organization) estimates that $32 billion of sales were of counterfeit drugs [3]. Counterfeit drugs, defined by the FDA (Federal Food and Drug Administration) are drugs which that are deliberately and fraudulently mislabeled with respect to its true identity and source. It is categorized by drugs that:

- have wrong, less or no active ingredients
- is a different drug than prescribed
- is an unapproved or unauthorized version of the legal one

Criminals get a substantial amount of profit from counterfeiting drugs, even more so than dealing narcotic substances like heroin and ecstasy. WHO states that the U.S. spent $203 billion alone on prescription drugs [3]. Even if counterfeiters could get just a very miniscule portion of that, they would easily make a fortune.

Top Drugs Counterfeited

1. Combivir® (lamivudine/zidovudine)
2. Diflucan® (fluconazole)
3. Epivir® (lamivudine)
4. Epogen® (epoetin alfa)
5. Lamisil® (terbinafine)
6. Lipitor® (atorvastatin)
7. Norvasc® (amlodipine besylate)
8. Procrit® (epoetin alfa)
9. Serostim® (somatropin, mannalian derived)
10. Sustiva® (efavirenz)
11. Trizivir® (abacavir/lamivudine/zidovudine)
12. Viagra® (sildenafil)
13. Zerit® (stavudine)
14. Zyprexa® (olanzapine)

[4]

The most counterfeited drugs are those that are highest in demand and most expensive to produce. Combivir is a HIV medicine and about six tablets retails for about $600. Thirty-six tablets of Zofran, an anti-nausea drug can retails for about $500. Epogen is a counterfeiter’s goldmine: A concentrated form of Epogen can sell for $5,000 a bottle [1].

Counterfeit Drugs: A Rising Health Risk
Counterfeit prescription drugs are a serious threat to public health. The victims are mostly people who need frequent and serious medication like cancer patients, AIDS patients and patients with heart disease. And the problem is getting worse too.

[2]

The rise of counterfeiting over the years can be broken into two major factors. One is the growing involvement in the drug supply chain of under-regulated wholesalers and re-packagers. Ideally, before a patient picks up a prescription at the pharmacy, the drugs should have traveled from the factory to a reputable wholesaler, who would then sell it directly to the pharmacy. However, wholesalers are more likely to trade shipments with other wholesalers several times before it reaches the patient. Some of the wholesalers could be trading counterfeit drugs intentionally or not in these transactions, for profit. Another is the increase in online pharmaceutical sales of imported drugs. Drug sources from online sales are difficult to determine. Many foreign pharmacies sell drugs to countries like the U.S. at an attractive price where it is illegal to buy in pharmacies without prescriptions. Unknown and unapproved drugs are then entering the country, some of which could be counterfeit. Foreign sellers claim to have certifications and licenses to sell quality drugs, and although they may be approved in their country, it may not be approved in the United States through the FDA.

Counterfeit Drugs: The Impact on Public Heath & Pharmacy
Counterfeit products may include drugs with no active ingredient, with an insufficient quantity, with the wrong active ingredient or with fake packaging. Individuals who receive counterfeit medication may be at risk for a number of serious health consequences. Patients may experience side effects, allergic reactions, or even a worsening of their health condition. In one case, an 18 month baby was given Neo-Melubrina (dipyrone) in a backroom clinic in Tustin, CA. The drug is illegal in the United States due to its high risk for potentially fatal side effects. Unfortunately, the baby died just days after the treatment. These drugs are known to have been smuggled from Mexico to Southern California. An even more
serious case occurred in Niger. Over 50,000 people were inoculated with fake vaccines during the meningitis epidemic in 1995. The vaccines were to be thought of as safe and came from another country as a gift. The gift resulted in 25,000 deaths [3].

Pharmaceutical companies also suffer from counterfeit medications. They must face the costs of litigation from patients who received counterfeit drugs and must bear the loss due to recalls. This also damages the public trust and confidence, and in turn reduces the investment in the pharmaceutical industry.

**California Prescription Drug Pedigree: Purpose**

In 2004, The California State Board of Pharmacy sponsored legislation (SB 1307) that made changes in the drug distribution system to protect against counterfeiting of drugs. The board is stating a requirement of an electronic pedigree to track each prescription drug at the saleable unit through the distribution system. This includes all imported and exported drugs in and out of California. The overall intent is to secure the drug distribution system and enable through heightened security a sustained and increased confidence in the authenticity and quality of prescription drugs. In 2006, they sponsored legislation (SB1476) which clarified pedigree requirements, and moved the effective date to 2009, to allow the industry sufficient time to implement electronic pedigrees [5]. Many pharmaceutical companies have complained that changing their entire supply chain would require more time. Mark O’Connell, president and CEO of Suplyscape, one of the biggest ePedigree solutions providers stated that “The senior vice president of McKessan sat in front of the board and said that of the 600 manufacturers that provide the company with drug products for the state, only 100 will be prepared by January 2009.” Dave Wilcox testified on behalf of NCPA (National Community Pharmacists Association) in front of the board to recommend delaying the implementation date to provide the necessary time to ensure full compliance [7]. In response, the board had announced in March 2008 that the effective date will be pushed further to January 2011.

**California Prescription Drug Pedigree: Rules and Requirements**

There are specific requirements that the State of California requires from all prescription drugs. One of which is the needed information in each container. The pedigree requires the following information:

- Source(s) of the prescription drug: information of sources of each link or stage in the distribution chain
- Prescription drug and transaction information: generic name, brand, dosage, container size, date of each transaction in the distribution chain, expiration date, etc.
- Prescription drug ownership information: business owner information, state license number, manufacturer’s information, shipping information, addresses of each affiliating business
- Certification of transaction authenticity: a certificate that the drug contained is true and accurate [5]

A pedigree must reflect every change of ownership from manufacturer until to the final sale. This means that the manufacturer initiates the pedigree and that each change in ownership throughout the
supply chain must be tracked. A change in prescription drug ownership is defined by the State of California as:

- A sale, trade, or transfer of prescription drugs between a manufacturer and wholesaler;
- A wholesale sale to a pharmacy, other wholesaler, clinic or prescriber (including the practice of “wholesale brokering” where a wholesaler does not take possession of a prescription drug but makes arrangements for the delivery of a prescription drug and processes the paperwork);
- Drop ship deliveries by or for a manufacturer, wholesaler, pharmacy, or prescriber;
- Consignment transactions;
- Third party logistics (3PL) transactions;
- Repackaging transactions;
- Pharmacy sales to another pharmacy;
- Pharmacy or prescriber returns to a wholesaler or manufacturer;
- Pharmacy sales to a prescriber or other licensed entity authorized to receive drugs;
- Pharmacy, prescriber, or wholesale transfers to a reverse distributor.

It also requires that each drug must be tracked to the individual saleable unit. This means the smallest package that is received and distributed by the wholesaler, pharmacy or anyone administering or dispensing the drug must have a unique product label to track its information. For example, each bottle of 100 tablets in a case of 48 bottles is required to have a unique identification made at the point of its manufacture that corresponds uniquely to the pedigree record [5].

The State of California Board of Pharmacy has very strict requirements on what is needed on the pedigree, but they have not made any requirements on how businesses will implement such methods. The board has not placed any directions or technological requirements to abide the pedigree law. Although the intent of the original law was that RFID (Radio Frequency Identification) tags be employed, the law only mandates that the drug products be serialized with a unique identification. The law also does not mandate any specific kind of data carrier/tag or protocol for such carriers.

**California Prescription Drug Pedigree: Costs & Benefits**

The cost of implementing e-pedigree solutions in pharmaceutical companies, especially small ones, is enormous. The cost of implementing such technology in chain pharmacies have been estimated anywhere from $10,000 to 40,000 per location. One chain pharmacy stated that even once the plans of upstream trading partners are determined, an additional 15-18 months are needed to implement E-pedigree. Another claim by a large chain pharmacy expects to cost up to $54 million for one distribution center covering 591 pharmacies to completely implement end-to-end serialization [8].

Some obvious benefits of the California Prescription Drug Pedigree are increased protection against counterfeit drugs throughout the distribution system and increased confidence in authenticity and efficacy of prescription drugs. It will improve patient safety and public health by having wholesalers and
retailers to rapidly identify and report counterfeit drugs. Other benefits include better tracking of products and improved quality control in pharmaceutical companies.

This pedigree has also given an opportunity for high-tech companies to sell E-pedigree solutions to meet the laws set by California. Companies such as Nosco, HP (Hewlett-Packard), Systech International and SupplyScape have teamed to build fully compliant solutions incorporating RFID technology. More about this RFID solution will be discussed later.

**Florida Prescription Drug Pedigree: Differences**

Many other states have already made initiation to mandate pedigrees to prevent drug counterfeiting. The state of Florida has already amended in 2006 its Florida Prescription Drug Pedigree, which will require by law that every bottle of drug distributed by wholesaler must contain a full pedigree. It is the first state to fully enforce the law, with its intent to protect the public by safe guarding the drug supply. There are a couple of differences between the California Pedigree Mandate and the Florida Pedigree Mandate. One big difference comes with the definition of “pedigree”. In California, a “pedigree” is defined as an “electronic record, created and maintained in an interoperable electronic system, containing information regarding each transaction… through to the final sale to a pharmacy or other entity or person furnishing, administering or dispensing the drug to the patient.” In the state of Florida, it is defined as a “document recording each distribution of a given prescription (Rx) drug, from sale by manufacturer… until final sale to a pharmacy or other person administering or dispensing the drug” [31]. Florida’s pedigree requirements can be met either through paper or electronic documents as long as they comply with the record retention requirements, while California only accepts electronic pedigrees. Another key difference between the pedigree laws is at what occurrence would require an update on pedigree information. The California pedigree law would require pedigrees to update each change in ownership, which means that the movement of the product through the owner’s network facilities does not need to be included on the pedigree. The Florida pedigree law requires updates when there is a change in custody (physical possession), even when ownership has not changed. Also, California’s pedigree law is the only law that requires a unique serial identification for each unit. While most pedigree laws avoid specifying technology, including the specification for how certification is accomplished, Florida is the only state that specifies using FIPS (Federal Information Processing Standards) which uses the PKI (Public Key Infrastructure) for digital signatures for their electronic pedigrees. Differences in these pedigree laws pose a challenge for many pedigree solution companies. They must find a way to ensure that pedigrees can meet all requirements for each state accordingly as well as business requirements imposed upon the supply chain participants by laws and regulations. The GS1 Healthcare US Pedigree/ EPCIS Assessment Task Force are selecting a method to combine the Drug Pedigree Messaging Standard with the Electronic Pedigree Code Information Services to produce a pharmaceutical track and trace system suited for compliance and sharing of serialization data within the supply chain. The difference between laws creates 4 challenges for EPCIS:

- Change of ownership as opposed to change in custody
- Data elements required by pedigree laws
- Pedigree completeness
- Pedigree integrity, authenticity and non-repudiation
**RFID (Radio Frequency Identification)**

RFID is a method to automatically identify products by storing and receiving data using RFID tags and transponders. Today, RFID is used mostly for supply chain management to improve the efficiency of inventory tracking. With the rise in drug counterfeit cases and the California Prescription Drug Pedigree, the FDA states that RFID has become the promising solution to satisfy the mandate and combat counterfeit drugs.

The following flow diagram shows an RFID system, in the simplest form. The RFID tag is woken up by the RFID reader (interrogator), where the reader translates the signal to a language understandable to an application server. Middleware is the interface between the interrogator and the application software and information management system.

![RFID System Diagram](image)

**RFID (Radio Frequency Identification): The RFID Tag**

Passive RFID tag on Moisturizer and Active RFID tag on Harrier [12] [13]
The most important piece of hardware in RFID is the tag. Data can be printed or etched on an electronic substrate and embedded in the plastic tag. They can be classified by whether they are active, passive or semi passive. Passive tags do not have their own source of power, so their power comes from a fast electrical current induced by a frequency radio scan from an RFID reader. This makes their read range short but can be made as thin as a sheet of paper (practically 2D) and very cheap to purchase. Active tags, on the other hand, have their own source of battery, usually a very small battery that is continuously on and this provides them with longer ranges and the ability to store more information. With their own supply of power, they have longer read ranges but they are larger in size (must be 3D). Semi-passive tags also have a power source like active tags, but will only use power once a RFID reader sends a radio scan to wake it up. Below summarizes the differences between passive and active RFID.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Active RFID</th>
<th>Passive RFID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tag Power Source</td>
<td>Internal to tag</td>
<td>Energy transferred from the reader via RF</td>
</tr>
<tr>
<td>Tag Battery</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Availability of Tag Power</td>
<td>Continuous</td>
<td>Only within field of reader</td>
</tr>
<tr>
<td>Required Signal Strength from Reader to Tag</td>
<td>Low</td>
<td>High (must power the tag)</td>
</tr>
<tr>
<td>Available Signal Strength from Tag to Reader</td>
<td>High</td>
<td>Low</td>
</tr>
</tbody>
</table>

Tags can also be classified by their frequency: low frequency (LF), high frequency (HF), ultra high frequency (UHF) or microwave. The power levels and regulations for usage vary with each country, but none of them require a licensing fee since the devices do not raise any serious threat of RF interference with other devices. The table below shows how different RFID tags are preferred in certain uses and industries over other types.

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Read Range</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Applications</th>
</tr>
</thead>
<tbody>
<tr>
<td>LF (124 &amp; 134.2kHz)</td>
<td>Passive &lt;10cm</td>
<td>No affected by liquids, low cost</td>
<td>Low read range, slow transmission</td>
<td>Animal identification, automobile anti-theft systems</td>
</tr>
<tr>
<td>HF (13.56MHz)</td>
<td>Passive &lt;1m</td>
<td>Can work with metals, low cost</td>
<td>Low read range</td>
<td>Smart cards, Vehicle Immobilization</td>
</tr>
<tr>
<td>HF (433MHz)</td>
<td>Active</td>
<td>Balance of low cost, size, and frequency</td>
<td>Limited life span, high cost</td>
<td>Access Control, Air Cargo</td>
</tr>
<tr>
<td>UHF (868 to 956MHz)</td>
<td>Passive &lt;10m</td>
<td>Longest passive</td>
<td>Complex base</td>
<td>Tracking vehicles</td>
</tr>
</tbody>
</table>
The technical capabilities between active and passive RFID tags are very different, and selecting the right kind of tag to fit a certain application needs extensive knowledge of its requirements and the tag’s capabilities. 4 major factors separate the two kinds of tags:

1. Communication range: Passive RFID has shorter range because it needs very strong signals to power the tag, limiting only a small amount of power for the tag to respond to the reader. Passive RFID typically have a range of 3 meters or less. Active tags have no restraint on power due to its battery source, and therefore are capable of read ranges of 100 meters.

2. Multi-Tag collection: Collecting multiple tag readings within a single operation is difficult using passive tags, due to its limited communication range. For example, a forklift containing a pallet of tagged items would require an immense amount of communication between the reader and the tags. Because each interaction between reader and tag takes time, and the communication range is about 3 meters, the chance of interference is high with more tags causing passive tags to be disadvantageous. Thousands of active tags can be read by a single reader since the operating range is about 100 meters.

3. Sensor capabilities: Active tags are constantly powered, meaning they are always on and alert. Some applications like ice cream vendors may install RFID tags on their products to check that their products are below a certain temperature. Active tags have the ability to do constant monitoring, where passive tags cannot.

4. Data Storage: Both tags can store data in the tag, but passive tags do not have their own power source, so they usually only contain 128bytes (1000bites) or less of data. Active tags have the capability to store larger amounts of data with 128Kbytes (1million bytes) of data and can send longer data packets to retrieval [14].

EPC global is an organization to set up a standard for adopting EPC (electronic product code) technology. The main focus of EPCglobal is to create a world-wide standardized for RFID. They have categorized RFID tags into 4 classes:

<table>
<thead>
<tr>
<th>RFID Class</th>
<th>Active or Passive</th>
<th>Capabilities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class 0 and Class 1</td>
<td>Passive</td>
<td>Backscatter, Low cost</td>
</tr>
<tr>
<td>Class 2</td>
<td>Passive</td>
<td>Backscatter, Low cost, for security</td>
</tr>
<tr>
<td>Class 3</td>
<td>Semi-Passive</td>
<td>Backscatter, 100m range, more functionality than Class 2 or Class 1</td>
</tr>
<tr>
<td>Class 4</td>
<td>Active</td>
<td>Active transmission, 100m</td>
</tr>
</tbody>
</table>
RFID (Radio Frequency Identification): The RFID Reader


The RFID reader typically contains a module (transmitter and receiver), a control unit and an antenna. The reader has three main functions: energizing, demodulating and decoding. Readers can also translate the RF waves received by the RFID tag and then translate the information to another system like a computer or a logic controller.

The RFID readers should be made to the user to provide the best fit, form and functionality. There are a wide range of reader types, and the best way to explain each of them is to first define the situation in which a specific reader is preferred.

<table>
<thead>
<tr>
<th>Purpose</th>
<th>Reader Type &amp; Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conveyor Reading</td>
<td>Case-level tracking on conveyors using multiple antennas</td>
</tr>
<tr>
<td>Dock door/Portal Reading</td>
<td>Portal Readers for pallet-level tracking with metal meshes to prevent mixing of RFID signals</td>
</tr>
<tr>
<td>Stretch Wrap Station Reading</td>
<td>Fixed readers to read information on tags on individual items</td>
</tr>
<tr>
<td>Overhead Reading</td>
<td>Fixed readers, positioned on top of the RF surface, for bulky items, and being transported by a forklift</td>
</tr>
<tr>
<td>Handheld Reading</td>
<td>Mobile handheld readers for maneuverability and selectivity</td>
</tr>
<tr>
<td>Forklift Reading</td>
<td>Portal readers for reading pallet-mounted and pallet-racking tags</td>
</tr>
</tbody>
</table>
RFID (Radio Frequency Identification): EPC and the Central Database

RFID tags contain a limited amount of information. One of the most important pieces of information is the tag is the EPC (electronic product code). The EPC is a numbering scheme that uniquely identifies the object that is tagged. EPC is used to store information about the product in an external database, so that only the EPC number is stored in the tag memory. This allows maximum use of the tag’s memory as well as a lower cost for the tag. The EPC consists of 3 sections: The heard and EPC-manager, object class and serial number. Below is a sample of a 96-bit EPC.

```
8 28 24 36
```

The header (tag version number) identifies the length, type structure, version and generation of the EPC. The EPC manager number (domain manager) is responsible for maintaining the subsequent partitions. The object class identifies a class of objects and the unique identifier is the serial number that identifies the instance. The EPC is structured in bits, consisting of binary code (0’s and 1’s). There are multiple formats including various bit lengths (64 and 96 bits) and all formats support unique EPCs [21].

The information behind each other with an RFID tag is stored in a central database. This is done through the EPC network. It was designed to provide a linkage between all physical data and EPC tags worldwide. The entire chain of the EPC network consists of the RFID tag, reader, the Savant, ONS and the PML server. Below outlines the EPC network and the capabilities.
form factors that carry the EPC

<table>
<thead>
<tr>
<th>Readers</th>
<th>The data capture device; portable or fixed (installed), connected to a Savant or network</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPC (electronic product code)</td>
<td>the code carried by the data carrier; the globally unique pointer for making enquiries about the item associated with the EPC</td>
</tr>
<tr>
<td>Savant</td>
<td>Servers which act as local repositories for EPCs and associated information, and which support sophisticated, flexible middleware for serving PML queries.</td>
</tr>
<tr>
<td>ONS (Object Name Services)</td>
<td>the distributed resource that “knows” where information about EPCs is held (just like DNS).</td>
</tr>
<tr>
<td>PML (Physical Markup Language)</td>
<td>like XML, with XQL query structure to allow structured querying and reporting of EPCs and attributed data.</td>
</tr>
</tbody>
</table>

**RFID in the Pharmaceutical Industry: RFID Technology**

**Selecting RFID Tags**

There has been much discussion about the potential of RFID in the pharmaceutical market. Much of the focus has been using passive tags in the ultra-high frequency (UHF) band due to the Wal-Mart RFID mandate for case and pallet level tracking, leading to the global standard of using EPC Gen 2 UHF tagging. But in the pharmaceutical industry, choosing the right RFID technology for each level of tracking is critical. The method to decide on the right technology is based on several factors including the environmental in which the containers are in, the size and form factor, read range, cost, and security.
Item Level Tracking

Individual items will be required to have a pedigree in accordance to the California Pedigree Mandate. Many studies have been made as to what kind of RFID technology shall be implemented in item-level tracking and after much debate (still on-going), the implementation of NR (near-field) UHF is becoming more prevalent but have not been fully integrated. NR UHF is a hybrid between standard UHF and HF tags, which combines the standard UHF Gen 2 chip in UHF tags and the antenna design to communicate by Near Field like the HF antennas. This takes the best of both HF and UHF capabilities into a single tag.

Read Range and Read Zones

NF UHF tags have also been proven to work in close proximity much like HF tags. Read range is not a function of the frequency or the protocol, rather it is the tag and reader antenna design and RF power. UHF has flexibility to provide both near and far field ranges. HF tags require many turns or stamped or etched copper that creates a larger mass than UHF. UHF tags have powerful near-coupling, which requires only a small loop antenna, and with its reduced mass and magnetic shielding, it can become more visible in large populations in small proximities. In an multi-tag reading experiment, Impinj attached NR UHF tags directly onto the center of DVDs and read through a stack of fourteen of them. In the case of multi-tag reading of over 30cm may require the NR UHF to operate at FF (far-field) which will produce reliability reads inferior to HF. The Gen 2 standards in UHF tags provide anti-collision algorithms that allow faster and more reliable reads, up to 5 times and the Magellan form of HF is the only comparable type that can compete with the UHF read rate.

Liquids and Metals

Item-level drugs can be susceptible to liquids or can be in a form of a liquid themselves. Near-field RFID uses a magnetic field to power tags, which will not be absorbed in fluids such as water, lotion and shampoo. With UHF’s magnetic field and electronic field capability, the tag can be made to work with metals and actually allow it to couple the electric field into the tag when properly designed. For example, Tyco implemented UHF tags right under EAS tags (Electronic Article Surveillance) so the metal in the EAS tag can enhance the performance of the UHF tag.

Form Factor and Tag Size
UHF tags do not have a size constraint. Smaller tags will have shorter read ranges, while larger tags will have longer read ranges. The antenna size is the only component that dictates read range and for item-level tracking, a small size tag is sufficient. UHF is a simpler mechanical structure and can withstand bending around small items like bottles and vials, just as much as HF of similar size.

**Cost**

HF tags require highly conductive coil antenna coiled into many loops do develop the required voltage to power the chip. UHF tags have a simpler antenna design and its frequency is 70 times higher, providing more energy with just a single loop. This leads to two reasons why UHF tags are less expensive. HF tags need more metal to print or etch the loops onto the tag. This also means the complexity of manufacturing the tag is greater than UHF. NR UHF tags cost about 5-10 cents, while HF tags cost roughly 1 cent more for the same specifications. The prices of RFID interrogators play an important role in cost. The lowest UHF reader is about $150, while an HF reader can cost as low as $15, therefore the bottom line costs have not been fully proven.

UHF Antenna, 1 layer 9mm (left), HF Antenna 2 layers 12mm (center) and Close up of HF Antenna (right). [24]

**Security**

Both UHF and HF can provide the same level of security and are not limited by frequency. Gen 2 provides built-in security measures including 32-bit access and kill password protection, cover-coding of transmitted data, and more. The level of security will only depend on cost. Adding more security means adding computing power which increases the cost of the tag.

**Standards, Protocols and Regulations**

There are drawbacks to implementing UHF, especially when implementing it globally and into already standardized applications like cell phones or military applications. HF tags have a much broader applications like tickets, passports, cards, conveyances, libraries, and lie within protocols such as ISO 18000-3, 15693 and 14443. ISO 18000-6 Gen 2 is the only UHF protocol. In other countries the power levels and bandwidth constraints are problematic in UHF. The chance of interference is considerable,
including between readers in the same system in European and Japanese radio regulations (for example). In conclusion, although NF UHF carries a wider range of capabilities and in the future will come at a lower cost, it is not yet practical under radio regulations of many countries and it has not yet fully proven a commercial reality, therefore many major drug manufacturers like Pfizer, GlaxoSmithKline, AstraZeneca, and others have stayed with HF for best performance.

Case Level Tracking
FF UHF tagging is the more dominant method for case and pallet level tracking than HF. UHF tags typically operate using electromagnetic coupling which is better suited for long-range reads (6 inches to 18 feet). This allows a wider view at the distribution process.

Implementing RFID in the Pharmaceutical Industry

Drug counterfeiting and patient safety is of high concern in determining the method of implementation of RFID. There are many ways an RFID tag can be imbedded into an individual item. Pfizer uses small (9mm) NR UHF tags that are attached to the product package, but there are other methods. Many vendors of RFID inlays (the tag, antenna and substrate) have teamed with label converters to create production-line-ready assemblies that can apply the tags simultaneously with the label.

Some companies like Impinj are incorporating the tag into the bottle or cap that would be dispensed in. This features a stronger defense against counterfeiting, since it would be essentially impossible to extract the tag from the bottle. In 2005, TAGSYS announced a cooperative agreement with West Pharmaceutical Services to implement RFID tags into the closures that West provides for syringes. This is a good measure to not necessarily prevent counterfeiting but for the ultimate goal of patient safety. Doctors or clinicians that administer shots with syringes can have it verified through RFID to ensure the patient is getting the right drug. Medication errors like these are an unfortunate occurrence but these incidents are not uncommon. Chances of errors during distribution, repackaging and at the point-of-use are reduced from the use of RFID and its track-and-trace capabilities. Secondary seals are a feature in bottles and vials that prevent tampering but have also provided room for RFID technology. Secondary seals are the closure system that does not come into direct contact with the drug. It consists of an aluminum seal crimped over the vial and stopper and is topped with a plastic flip-off button. It gives multiple layers of protection and space for drug information to be molded into the button or

Enhanced patient safety with point-of-use instructions and identification can help prevent in-process errors. Printed seals help authenticate products to inhibit improper labeling and enhance patient safety.
embossed on the shell with RFID. Furthermore, molding a tag into the plastic button rather than within the label overcomes a problem with RFID label technology. Tags close to liquids are more difficult to read because liquids interfere with signals transmitted by the tag.

Middleware and Database in the Pharmaceutical Industry

Middleware applies the filtering, formatting or logic to the tag data captured by the reader so the data can be processed by a software application. When it comes to drug manufacturing and combating counterfeit drugs, item-level security and data encryption is important. Companies like SkyteTek implements two security features like Advanced Encryption Standard (AES) and Secure Hash Algorithm (SHA). This allows the tag data to be scrambled so that unauthorized parties cannot read it. In item-tracking of pharmaceuticals, RFID is becoming a bigger target for hacking and the added security is necessary. IBM’s Solution for Pharmaceutical Track and Trace software features full item level serialization with track and trace capabilities, and at the same time ensures patient safety and compliance with government mandates like the California Prescription Drug Pedigree. The middleware product is IBM’s WebSphere RFID Information Center, which is built on specifications for the EPCglobal Information Services (EPCIS), which provides a framework for supply chain partners to exchange EPC-related data through the standardized EPCglobal network.

IBM’s Solution For Pharmaceutical Track & Trace compliance with California Mandate[26]
Implementation Challenges

Implementing RFID involves multiple challenges. Deployment of RFID in a pharmaceutical company is a complex project and can take time and money, which many are hesitant to invest in. The big challenge to all companies continues to be the cost, but is also due to the following reasons:

- Resistance to change – Many rely on manual processing or barcode scanning to track items. When moving from an old technology to a new one, this requires a change in business standards and procedures.
- No one size fits all – RFID systems are customized for each deployment.
- Multiplicity of vendors – RFID systems require multiple sources to be assembled, which can create integration obstacles and compatibility issues.
- Resistance to information sharing – When prescription drug information must be transferred over from manufacturer to wholesaler to pharmacy, these trading partners must all be able to resolve any information sharing problems.
- Lack of skilled personnel – RFID knowledgeable IT personnel may not be available everywhere to aid in any implementation
- Privacy Issues – There is a fear from patients that RFID will violate consumer privacy and that such personal information may be used or accessible to the wrong hands. Although the fear isn’t practical, there are still voices that address the concern to companies.

How RFID Protects the Pharmaceutical Supply Chain and Patients

The most effective way to show how RFID provides security during manufacture, distribution and administration is to look at how a RFID-equipped pharmaceutical drug from the drug manufacturer gets to the patient through the supply chain [30].

First, the manufacturer assigns a unique EPC number to each product to allow track and trace throughout the supply chain. Next the packaging supplier writes on the tag the EPC number assigned by the manufacturer and embeds the tag into the packaging materials.

Next the raw materials are tagged to allow the product’s pedigree to extend

Then the manufacturer receives the materials and records the EPC numbers into the database, which will link the raw materials to the product’s EPC and pedigree. This is also a checkpoint to make sure that only products with valid EPC numbers get processed through the supply chain. The manufacturer also assigns unique EPC numbers to cases, cartons and pallets and other higher level items.
In the case of pharmaceutical drug kits, it can be either tagged or untagged products. If necessary, a kit can be assigned its own EPC number.

Sharing data between trading partners removes the burden of collecting and storing every detail. The EPC number serves as a key to ensure an exact match between products and their drug information. Security rules prevent unauthorized parties from accessing confidential data. Sensors can be embedded to record conditions throughout the supply chain and can be added to the product’s history.

Before products arrive to the wholesaler, ASN (Advance Shipping Notices) can inform the wholesaler about the shipments before the products arrive. RF scans of incoming shipments can verify the products match the EPC data.

When it reaches the pharmacy, prescription errors are avoided when the data associated with the product’s EPC is automatically compared to the customer’s medical records. Once it has been purchased, a POS system detects that it has left the supply chain and deactivates the EPC number, but the database still retains the information.

When products arrive at a hospital, administering errors can be avoided by scanning patient ID and drug EPC number to automatically compare the associated information and also check the pedigree and expiration date to make sure it matches the patient’s needs. RFID readers can be placed on recycling bins to detect the tags of discarded or finished products to notify the database that the product has reached the end of the supply chain.
Other Methods to Prevent Drug Counterfeiting

There are other technologies in use today to provide security and tamper detection of drug products. Some of its security measures are the drug resistant packaging in items. In bottles of the anemia drug, Procit, manufactured by PSGA, it is custom-designed uses color coding and covert printing to help fight counterfeiting. Seal colors and the plastic flip-off buttons match colors on the label to help identify the drug as authentic. Printing on the button also describes the contents and printing on the seal shows the brand name and dosage strength. Such printing stays hidden from the user till the button is removed. Another major drug manufacturer, Amgen, uses custom buttons as an anti-counterfeiting measure for their drug Epogen. It is molded with the Epogen logo, along with dosing and strength information. It also uses colored seals to differentiate single from multi-doses of the drug. Color-coded seals have also been used for buttons in plastic vials of Diflucan, a drug made by Pfizer that was counterfeited in Japan.

The printing contains Japanese characters with drug information which will also help distinguish between other drugs with similar names and prevent medication errors. Other technologies include spectroscopic inks and high-quality, full-color graphics. Information on bar codes, for example, can be printed on buttons in colored inks that are readable only under special lighting. High-quality graphics authenticate the drugs as genuine. More sophisticated measures of security make the technology more difficult for drug counterfeiters to duplicate.

Current RFID Solutions

Many pharmaceutical manufacturers have already announced large-scale programs for item-level product tagging. They see clear advantages of implementing RFID technologies to fight counterfeiting and boosting revenue and supply chain efficiency by switching to unit-level tagging. In 2006, Pfizer deployed a full scale RFID project to track all bottles of Viagra sold in the United States. They implemented mass serialization using HF Gen 2 RFID 2-D bar code tags technology over UHF tags. A typical pharmaceutical pallet can contain up to 5,000 individual saleable units in combinations of packing, which may contain high levels of metal and liquid contents. Under these conditions, HF tags prevail over UHF in readability and universality [21]. In that same year, GlaxoSmithKline (GSK), one of the largest producers of AIDS treatments has worked with IBM to begin distributing bottles of Trizivir tagged with RFID technology to fight counterfeiting. Their primary goal is to fully authenticate the Trizivir product, with sales reaching $302 million in 2005 [21]. After testing in the supply chain, they have found out HF tags performed better at the unit-level while UHF performed better at the case-level.
In 2007, SupplyScape, Nosco and Systech International have teamed up with HP to announce the first complete RFID solution against drug counterfeiting for pharmaceutical companies. The full solution in one combines the latest 2D- and RFID-enabled packaging components and systems with serialization and tracking, and integrates these components with the client’s existing ERP and enterprise applications. In addition, it will also help companies be in full compliance with upcoming California ePedigree law. Each company has a certain role in implementing the RFID solution. HP guides the architecture, ERP/WMS integration and project services for the solution, and also manufactures the digital press technology used to print the serialized label. Nosco is a major packaging provider for pharmaceutical manufacturers and provides the packaging solutions. SupplyScape is the leader in serialization and ePedigree and delivers the ePedigree data management system. Systech brings the packaging-line serialization expertise to the solution framework [22].

<table>
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<tr>
<th>QC Process Steps</th>
<th>QC Failure Rate</th>
<th>Read Yield</th>
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<tbody>
<tr>
<td>Shipment from Converter</td>
<td></td>
<td>100%</td>
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<tr>
<td>Item Rejections because of HF RFID (all causes)</td>
<td>5 in 1,000</td>
<td>99.5%</td>
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<tr>
<td>Item Rejections because of 2D barcode</td>
<td>3 in 1,000</td>
<td>99.7%</td>
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<tr>
<td>Case Rejections because of HF item aggregation*</td>
<td>4 in 10,000*</td>
<td>99.9%*</td>
</tr>
<tr>
<td>Case Rejections because of UHF Gen1 tag**</td>
<td>3 in 100**</td>
<td>97%**</td>
</tr>
<tr>
<td>Case Rejections because of linear barcode</td>
<td>2 in 100</td>
<td>99%</td>
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Table 1. Performance data from Pfizer’s use of RFID for vaccines.

* Based on 40 HF reads/case.
** Duplicate-code issues and void label failure rates omitted.

[21]
IBM and TAGSYS are also implementing RFID technologies for item level serialization. Serialization is the first step towards compliance with California’s drug pedigree mandate and improving supply chain performance. The two companies will be providing the hardware, software and services needed to validate the performance, reliability and cost-effectiveness of RFID. Their first product is targeted for small-scale pharmaceutical companies called the Serialization Pilot Kit.

IBM & TAGSYS Serialization Pilot Kit

Hardware:
- 50,000 HF TAGSYS tags for item level serialization
- 1000 UHF TAGSYS tags for case level serialization
- TAGSYS HF reader stations (based on L400 Long Range Reader) with integrated diverters
- HF/UHF stations for association items from cases, and UFH RFID printers to print case labels.

Software:
- IBM WebSphere Premises Server software to manage RFID data capture process, associate items with production run data and generate serialization reports

Services:
- All necessary duties to install and setup the system

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<th>IBM Serialization Pilot Kit Workflow</th>
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<td>Preproduction</td>
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<td>Off line</td>
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According to IBM and TAGSYS, this solution can be deployed in under 4 weeks for $125,000. This kit will be available December 2008. This kit can also be upgraded to IBM’s full Solution for Pharmaceutical Track & Trace. The full solution automates event capture by integrating into real-time operational systems, incorporates receiving and pick-pack-ship processes for distribution centers, and configures IBM’s WebSphere RFID Information Center’s new ePedigree feature to meet California pedigree requirements.
The Serialization Pilot Kit offers a very prompt deployment of 4 weeks, but Omron Corp has put together a “One Day Compliance Package” that includes reader/writer, antenna, RFID printer accessories, training, and 10,000 RFID labels to get started. All this for under $20,000. Their goal is to achieve immediate compliance with any retail or DoD mandate that requires RFID tags on cases and pallets [29].

New in Pharmaceutical RFID Technology

RFID design and technology is constantly being improved and optimized for successful enterprise-wide RFID applications, especially in the pharmaceutical world. The leading UHF Gen 2 RFID solutions provider, Impinj recently unveiled Monza 3 tag chips with high-performance tag read and wire reliability with:

- 40% improvement in tag read sensitivity, increases readability of tags of items and materials in such environments as metals, liquids and dense packed cases and pallets
- 2x improvements in tag write sensitivity, improves item-level serialization efficiency and reliability
- Dual antenna input configuration, allows greater flexibility in orientation and position, increasing tag readability

In pharmaceutical manufacturing and fill-line applications, a NR UHF Gen 2 RFID solution consisting of Impinj’s Speedway reader and Owen-Illinois (O-I)’s item level embedded RFID tags powered by Monza chips achieves reading rates of up to 600 tags per minute (typical fill line operates at 250 to 300 bottles per minute) on bottles of many dose types: liquids, gel caps, solids and powder.

Alien Technology demonstrated their new Alien H3 IC for passive UHF RFID and Intelligent Tag Radar (ITR) Reader Platform. The Alien H3 (Higgs-3) IC features extended memory and unique authentication security features. The new Alien H3 IC supports various memory configurations, and up to 496-bits of EPC data and up to 512-bits of user memory. Based on benchmark testing, the Alien provides a 50% increase in sensitivity and 25% more than the Alien H2 IC (which powers the Squiggle). The H3 has a 64-bit UTID (unique Tag ID) which is programmed at the manufacturer and cannot be altered. This is good security measure to prevent counterfeiting, diversion and return fraud of pharmaceutical products. ITR provides information about the velocity and position of tags, in addition to the contents of tag memory. In the ITR platform is the ITR-Singulation feature which enables to reader to easily discriminate between adjacent tagged objects on a conveyor such as the manufacturing or packaging of pharmaceutical drugs. Other features include ITR-Velocity, ITR-Directionality and ITR-Range.
Covidien is a leading global healthcare products company that creates innovative medical solutions for better patient outcomes and delivers value through clinical leadership and excellence. Covidien manufactures, distributes and services a diverse range of industry-leading product lines in four segments: Medical Devices, Imaging Solutions, Pharmaceutical Products and Medical Supplies. In May 2008, the FDA has approved Covidien Imaging Solutions’ contrast delivery system integrating RFID technology. The delivery system combines the unit-dose Ultrajet prefilled contrast media syringes with its Optivantage DH power injectors to provide the only RFID-enabled contrast delivery solution available in the United States. The RFID will transmit data between the Ultrajet syringe and the Optivantage DH power injector with RFID readers. Information will include drug information and can check if the drug is past its expiration date. The injector can also physically alter the RFID label on the syringe once it is used, which would prevent injection of contents from a previously used RFID syringe. This will enable radiology technologists to better ensure that each patient receives the prescribed drug and drug dose during a procedure [32].
Questions and Answers for Aaron Graham and Michael Celentano from Purdue Pharm L.C.

The following questions and answers were addressing concerns regarding the issues of drug counterfeiting and how the implementation of RFID has helped patient safety and supply chain management in Purdue Pharma L.C. Aaron Graham is the Vice President & Chief Security Officer of Pure Pharma and Michael Celentano works in the IT group of Purdue Pharma.

Q: What kind of RFID technology is used for each level or tracking?
   A. We are using UHF Gen 2 RFID technology to serialize at both bottle and case level

Q: At what points in the distribution system do you take reads on tags?
   A. First, we take reads at several in-house locations:
      1) First read is during packaging operation, post-label application. Each bottle is individually read to check that the tag is functional
      2) Second read is during packaging operation, post-case packing. All bottles are read simultaneously in a 48 ct case, as well as the 1 case tag. Thus, a total of 49 tags are read, parent/child relationships are established, data is located into a local database.
      3) Third read is at the distribution center, outbound shipments. Case RFID tags are scanned to pallets and affiliated to outbound shipments. Data is collected again, and records are established to identify where each unique bottle and case was shipped.

Q: What kind of data do you write on the tag(s)? What data formats do you use?
   A. We write only a serial number in SGTIN 96 format.

Q: What middleware do you use?
   A. Device management and serialization control software from several vendors.

Q: Do you have any reports or statistics on the use of RFID in supply chain management?
   A. Approximately 3.5 billion bottles to date, 99.985% performing tags, with no problems reading 48 ct cartons and no significant impact to packing cycle times. In recent investigations working law enforcement nationally, we’ve been able to identify diverted or stolen bottles in three separate cases. In essence we’ve created a partial de-facto e-pedigree and it’s great evidence of the full potential for e-pedigree, patient safety and public health as a result of RFID