Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
November/December 2007, Vol. 27 No. 6



# Drug Pedigrees: Your Supply Chain Needs Them. Are You Ready?

by Norm Howe, Stephen Goldner, and Chris Fennig

**This article describes the challenges represented by counterfeit drugs and the consequences for companies that fail to recognize the threat to their value chain. It outlines the technical solutions that are available, assesses the merits of those solutions, and shows which solution fits best in different situations.**

## The Problem

The diversion of legitimate drugs and sale of counterfeit drugs is a significant drug industry problem, a law enforcement problem, and a health hazard to the world population. Dr. Scott Gottlieb, Deputy Commissioner for Medical and Scientific Affairs, US Food and Drug Administration, said in speech on 20 September 2005, "In 2000, the FDA opened six counterfeit drug cases, in 2003, we opened 30, and last year, we opened 58... Just this past month, on 31 August, we busted up a Lipitor counterfeiting and smuggling operation that was trafficking almost $50 million worth of the drug."

Studies by the World Health Organization estimate that counterfeit drugs are a $32 billion-a-year business. Counterfeit drugs have found their way into developed and developing countries alike. On 3 March 2006, Dr. Gottlieb spoke again on drug counterfeiting, "It has been estimated in the press that eight to 10 percent of the global medicine supply chain is counterfeit - a figure that rises to 25 percent or higher in some countries. Quantifying the problem is difficult because the counterfeiters do such a good job copying the genuine product and hiding their tracks, that it is hard to identify what is real and what is fake." Companies are faced with a growing threat to their brand value, the safety of their products, and to their bottom line. The industry is already paying the price of counterfeit drugs, but no one really knows what that cost is.

In 1987, Congress enacted the Prescription Drug Marketing Act (PDMA), which called for tracking and tracing of pharmaceuticals using paper pedigrees. The FDA, expecting that technical solutions such as Radio Frequency Identification (RFID) chips would progress more rapidly than has actually happened, has until now not enforced the legislation. In the absence of a Federal policy, it's been left to the states. Florida has taken the lead. Its law went into effect in July. California's law took effect 2 January 2007. Fourteen states have laws in the pipeline.

Drug manufacturers and distributors must now grapple with both an economic threat and regulatory chaos that will jeopardize their business. This article will define the problem, discuss the proposed solutions, and try to project the regulatory future.

## Background

Although the pharmaceutical supply chain is simple in concept, the reality is far more complex. Drug containers must be traceable from the factory, through distribution, all the way to the end user. In addition, the drug must be traceable at the item or primary container level despite the fact that the primary package may get aggregated into cartons, pallets, and shipping containers. When the primary container is hidden inside a carton, line of sight trace technologies become impractical. Compounding this is the complexity of the real world supply chain - *Figure 2*.

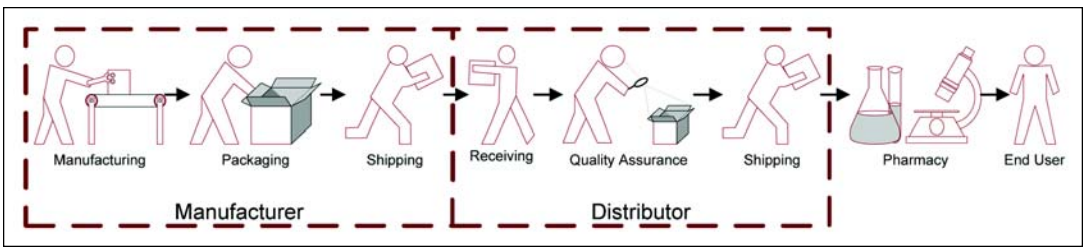


Figure 1. Conceptualized drug logistics flow.

*"The significant advantage of all types of RFID systems is the noncontact, non-line-of-sight nature of the technology."*

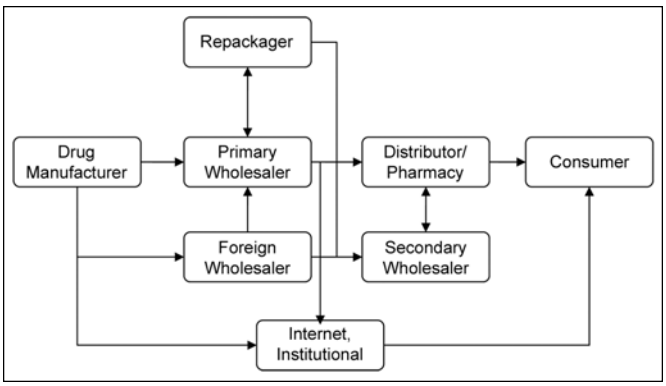


Figure 2. Actual drug logistics flow.

In 1999, the FDA published final regulations implementing the provisions of the PDMA. Both industry and Congress indicated a concern about the high cost of implementing these provisions and also raised a very real question of the seller's ability to obtain a transaction history from the prior distributors and the manufacturer. Consequently, the FDA decided to exercise enforcement discretion of the drug pedigree provisions, 21 CFR 203.3 and 203.50. In February 2004, the FDA again delayed the effective date of the drug pedigree provisions, this time until 1 December 2006, in part because it was informed by stakeholders in the US drug supply chain that the industry would voluntarily implement electronic track and trace technology by 2007. Although progress has been made, it is now clear that the use of electronic pedigree will not be widely adopted by 2007. As a result, in June 2006, the FDA announced that it did not intend to delay the effective date of sections 203.3 and 203.50 beyond 1 December 2006.

## The Solutions

The three contenders vying to be the solution of choice for drug pedigrees are paper, bar codes, and Radio Frequency IDentification (RFID). RFID is the technology that the FDA envisioned when it delayed the effective date of the drug pedigree provisions of the PDMA in 2004. However, RFID is not the only technology which could potentially solve the impending drug pedigree crisis. Bar codes and old fashioned paper are in the game; especially bar code systems, which are currently used on all shipments. But neither paper nor one-dimensional bar codes meet the need when one adds up the monumental amount of data that needs to be manipulated if traceability down to the item level is required. Two-dimensional bar codes can carry substantial amounts of data, but they cannot carry enough information to identify the drug down to the item level. Plus, they can be counterfeited more easily than the drug itself. Any type of bar code still has the operationally inefficient requirement of line of sight data capture so the bar codes cannot be hidden on the inside carton on a pallet, for instance. Also, the amount of time that it takes to scan a bar code is significant since only one can be read at a time by a scanner.

RFID tags come in a wide variety of shapes and sizes. Paper-thin tags, pasted onto books and files, can be hidden between pages. Tags can be screw-shaped to identify trees or wooden items, or credit-card shaped for use in access applications. The anti-theft hard plastic tags attached to merchandise in stores are RFID tags. In addition, heavy-duty 5-by 4-by 2-inch rectangular transponders which are used to track intermodal containers or heavy machinery, trucks, and railroad cars are also RFID tags. The type that is most applicable to the pharmaceutical industry comes in the form of razor-thin tags that are applied to product and shipping containers for purposes of tracking and identification.

The information encoded on the RFID tag can be read by an antenna and reader mounted on a dock door or carried as a hand-held. The antenna transmits a signal to the tag and the tag transmits its information back to the antenna. Unlike a paper-based system, RFID follows products automatically. With each transaction, whether it's the original filling of the primary container, packing into a carton, palletizing, or shipping, the package is scanned and the transaction is recorded. Each package has a serial number and once the bottle or the smallest serial-numbered part of the chain is opened, the pharmacy electronically flags that number. From that point on, if that serial number were to come up again in the system, i.e., if a counterfeiter tried to reuse that radio-tagged bottle, it would be clear that something is wrong. The significant advantage of all types of RFID systems is the noncontact, non-line-of-sight nature of the technology. Tags can be read through a variety of substances such as paint, cardboard, and other visually and environmentally challenging conditions, where barcodes or other optically read technologies would be useless. RFID tags also can be read in challenging circumstances at remarkable speeds, in most cases, responding in less than 100 milliseconds.

There are two general types of RFID technology; Active RFID and Passive RFID. The distinction lies with the way the RFID chip is powered. Active RFID chips are powered by an internal power source, a battery. Passive RFID chips are powered by energy transferred from the reader. Passive RFID chips typically store about 128 bytes of information, whereas Active RFID chips can store a thousand times as much, but can be as big as a carton of cigarettes. Because of cost and size differences, only Passive RFID chips are used for large numbers of items so we will restrict our discussion from here on to Passive RFID chips.

The RFID story is complex because even within the Passive RFID chip types there are subtypes that are competing to become the de facto solution for the Drug Pedigree prob-

| | PROS | CONS |
|---|---|---|
| **High Frequency (HF)** | - Maturity<br>- Water insensitive<br>- Global acceptance | - Short range<br>- Low data transfer<br>- Price |
| **Ultra High Frequency (UHF)** | - Long range<br>- Rapid data transfer<br>- Inexpensive | - Material dependent<br>- Regionally dependent<br>- Potentially harmful to drugs' structure |
| **Near Field UHF (NF)** | - Water insensitive<br>- Air interface is global<br>- Inexpensive | - Not in production<br>- Numerous frequency bands<br>- IP issues outstanding |

Table A. Pros and Cons of the three RFID technologies.[1]

lem. Based on the Pharmaceutical Benchmark (the only objective, scientific study of RFID for use in the pharmaceutical supply chain of which the authors are aware[1]), the three RFID contenders, **High Frequency (HF), Ultra High Frequency (UHF), Near Field UHF (NF),** each have their pros and cons - *Table A*.

The study analyzes the RFID use cases that need to be deployed in order to track and trace drugs throughout the pharmaceutical supply chain with RFID technology. HF can be used in close proximity to water, such as a vaccine vial, while far field UHF cannot. But UHF has a much longer reach than HF. Beyond 12 inches HF does not function, whereas UHF is effective up to 36 inches as reflected in Figure 4. In addition, UHF is more sensitive to the orientation of the chip relative to the antenna - *Figure 4*. UHF is the most appropriate technology for capturing tag data from cartons arranged on a pallet. Therefore, the supplier/distributor must be careful to deploy technology appropriate to each use case. Near Field UHF may be the single solution for the future, but is not yet ready for prime time.

No matter which technology is chosen manufacturers and distributors will have to make sure that their installations conform to FDA regulations. Each drug will have to be stability tested to ensure the signals do not degrade their potency and each drug company will have to get FDA approval for revised labels that contain RFID chips and revised bar codes.

## What Are Your Competitors Doing?

California's drug-pedigree legislation took effect on 1 January 2007. Amphastar Pharmaceuticals, in conjunction with its distribution partners, is implementing e-pedigree software. It is working to institute a system for tracking its drugs in the supply chain and verifying their authenticity. Because it manufactures primarily low-margin generic drugs, the company decided to use two-dimensional serialized barcoded labels instead of RFID tags to identify and authenticate its products. Amphastar considered using RFID technology for its e-pedigree system, as it knows RFID tags can automatically be read and matched against the serial number in the e-pedigree document, eliminating the manual scanning needed with bar codes. However, for most of its drugs, RFID tags are too costly. But that may soon change. The International Standards Organization (ISO) has approved the EPC Gen 2 Class 1 UHF standard, ratifying it as an amendment to its 18000-6 standard. Passage of Gen 2 as a global standard could foster greater competition in the passive UHF RFID systems market, thereby lowering RFID hardware costs for pharmaceutical companies and other end users, in the last 12 months, both HF and UHF tags have dropped in price significantly.

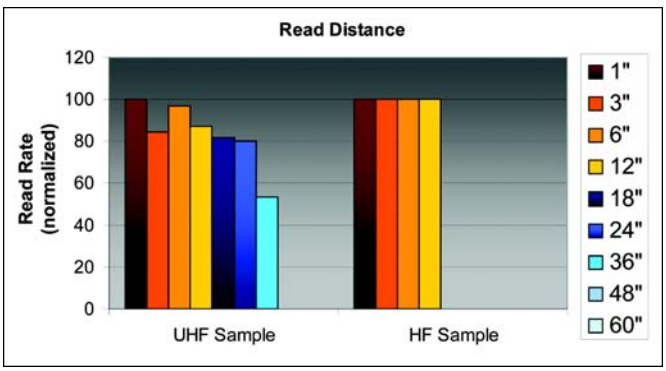


Figure 3. The effect of distance on read-rate for UHF and HF systems, courtesy ODIN labs.[1]

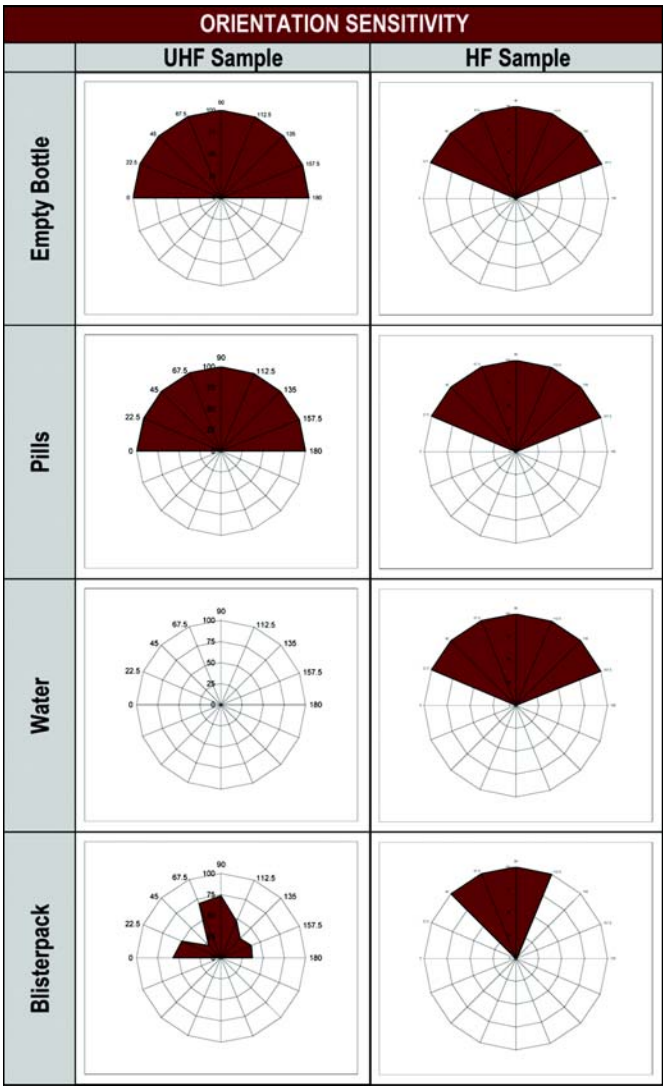


Figure 4. Orientation sensitivity of the RFID chip as a function of RFID technology and container type, courtesy ODIN labs.[1]

Considering a global drug (made in several countries and sold worldwide), Pfizer decided on HF technology for what is arguably the most famous public case of anti-counterfeiting. Their interest in RFID technology dates to a 2003 case involving bogus Lipitor. That very public case spurred Pfizer to participate in early FDA pilot programs. At a cost of approximately $5 million, Pfizer is putting HF RFID tags on bottles and cases, and UHF on pallets of another important brand, Viagra.

## Where Do We Go from Here?

Pharmaceutical companies must now ask themselves how they will respond to the Drug Pedigree challenge. There are really three questions that need to be answered. What technology will we use? How will our technological response be regulated? And what will it cost? We have discussed the technology question and unfortunately we cannot give you a silver bullet solution that you can roll out tomorrow.

On the regulatory side, the FDA has said that it will phase in its enforcement activities following a risk-based approach driven by four factors:

Factor 1 – High Value in the US Market
Factor 2 – Prior Indicators
Factor 3 – Reasonable Probability
Factor 4 – Other Violations of Law[2]

Whichever technical solution you choose beyond pure paper will have to be proven to be highly reliable using scientifically valid techniques. Any records that are explicitly required by the regulations that you choose to keep in electronic form will be subject to Part 11.

The only thing we can really predict about the cost of Drug Pedigree solutions is that they will be significant. The cost of chips, readers, antennas, and incremental labor can be estimated. But while the cost of RFID chips and readers may influence the choice of technology, that cost issue might turn out to be trivial compared to the cost of dealing with all the data that will be generated if all drugs have to be tracked at the item level into all USA distribution systems. That data will have to be transmitted and stored somewhere. Someone will have to write the software to flag inconsistencies. More significantly, no process has stepped forward to serve as the platform for the billions of transactions and the myriad methods of data recovery and transmission. The system can not run without a way to reliably store and transmit the data to all stakeholders: drug companies, wholesalers, retailers, and the FDA. Whether there is a satisfactory economic return on that investment will probably never be known because the costs that the solutions prevent, such as lost revenue, lost brand value, and product safety, are so hard to measure.

Lastly, even the best technical solution will not work unless the inconsistencies that the system finds are solved. Someone will have to act upon those inconsistencies and enforce legal action where necessary. Otherwise, all the hardware and software will have been installed for nothing.

## References


1. Summary findings from the *Pharmaceutical Item Level RFID Benchmark: Battle of the Frequencies* presented by Chris Fennig of ODIN technologies during his talk at *RFID for Pharmaceuticals* on 2 August. The full report is available at www.odintechnologies.com/store.
2. FDA "Draft Compliance Policy Guide 160.900 Prescription Drug Marketing Act – Pedigree Requirements under 21 CFR Part 203" June 2006.


## About the Authors


**Norm Howe** got his BS in chemistry at UC, Berkeley, and a PhD in chemistry at UCLA. He has held many management positions in the pharmaceutical industry, most in production. He has led a number of cross functional cost reduction, product development, and business optimization teams. Howe is a Senior Partner at Validation and Compliance Institute, LLC, a consulting firm which helps companies to comply with FDA regulations, and supplies expert witnesses. He is a member of ISPE and the American Chemical Society. For recreation, he likes to play golf, which he finds to be very cost effective on a dollar per stroke basis. He can be reached by telephone at: +1-734-740-9924 or by e-mail at: howen@vcillc.com.

Validation and Compliance Institute, 1529 Boxford Rd., Trenton, Michigan 48183, USA.



**Stephen Goldner** is the Founder and Principal Officer of Regulatory Affairs Associates (RAA) - a national leader in getting medical devices and drugs successfully approved by the FDA. A chemist and an attorney by training, He has more than 30 years of experience as a regulatory professional. Prior to forming RAA, Goldner served as the vice president of Regulatory Affairs for Ferndale Labs in Ferndale, Michigan. He also served as the vice president of Regulatory Affairs for ICN Pharmaceuticals, now Valeant Pharmaceuticals, in Costa Mesa, California. Throughout his regulatory career, he has developed both a strong track record of success and strong working ties with the FDA. These interactions have included work on NDA/ANDA, 510(k), IND submissions, QA/QC validation, and insured GMP compliance. Goldner is noted for his professionalism, knowledge, and ability to navigate successfully in the complex regulatory world of medical device and drug approval. During his prolific career, he has generated more than half a billion dollars in revenue for his various employers and clients. He is an active member of the Regulatory Affairs Professionals Society (RAPS) and serves on the board of MichBio. In addition to his passion for getting new medical devices and drugs approved, he enjoys traveling, reading, music, good food, and conversation, and is active in his faith community. He can be contacted by telephone at: +1-248-855-5595 or by e-mail at: sgoldner@regaffairs.net.

Regulatory Affairs Associates, LLC., 30833 Northwestern

Hwy., Suite 121, Farmington Hills, Michigan 48334-2581, USA.

**Chris Fennig** is responsible for leading strategic client engagements and R&D activity at ODIN technologies. He has focused on the emerging RFID industry since its inception and has successfully engaged leaders in the industry through his professional consulting services. His experience includes direct interaction with Wal-Mart's top suppliers, leading Aerospace companies, and global pharmaceutical companies designing and implementing novel RFID solutions. Fennig received his MS in physics entrepreneurship from Case Western Reserve University, a program dedicated to empowering physicists as entrepreneurs and his BS in engineering/physics from Taylor University in Upland, Indiana. He can be contacted by telephone at: +1-703-822-3776 or by e-mail at: chris@odintechnologies.com.

ODIN technologies, 22960 Shaw Rd., Suite 600, Dulles, Virginia 20166, USA.