

Radio Frequency Identification (RFID) in Clinical Material Supply Chain

Challenges and opportunities

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Summary

Starting with a general description on how RFID works and what applications have currently become common, the situation with pharmaceutical industry in applying this technology is considered.

Having analysed drivers and hurdles of implementation some potential of RFID application has been identified within clinical supply chain.

Following the “think big, start smart” strategy and embedded in thoroughly investigated business processes a pilot project named SIMPL (Standardization of Investigational Medicinal Product Labels) is described with solutions for and work-arounds of current hurdles.

Zusammenfassung

Radiofrequenz-Identifikation (RFID) in der Logistik klinischer Prüfpräparate

Nach einer einführenden Darstellung der Funktionsweise von RFID und dem gegenwärtigen Stand der Anwendungen wird die Situation in der pharmazeutischen Industrie näher betrachtet.

Nach gründlicher Untersuchung potentieller Vorteile und Hindernisse der Implementierung von RFID konnten einige Vorteile für die Anwendung in der Logistik klinischer Prüfpräparate identifiziert werden.

Auf der Grundlage sorgfältig untersuchter Geschäftsprozesse und der Strategie „Denken in großen und Beginnen in kleinen Schritten“ folgend wurde ein Pilot-Projekt mit der Bezeichnung SIMPL (Standardization of Investigational Medicinal Product Labels) gestartet. Die während dieses Projektes gewonnenen Erkenntnisse werden dargestellt.

Key words

- Radio Frequency Identification (RFID)
- Standardization of Investigational Medicinal Product Labels (SIMPL)

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1. Introduction

Continuous striving for process improvements and reduction of cycle times in order to serve the business objective “reduce time to market” has led to an in-depth evaluation of further technologies potentially suitable to serve this goal.

Based on thorough knowledge of business processes and workflows in clinical supply chain some areas have been identified, where current technological solutions used in other industries may provide opportunities for further developing and streamlining processes.

One of these technologies comprises application of RFID, the background of which and application within clinical supply chain is described in the following.

2. What is RFID?

2.1. Basic principle

RFID stands for Radio Frequency Identification. A basic RFID system consists of three components (Fig. 1):

- An antenna or coil
- A transceiver (with decoder)
- A transponder (RF tag) electronically programmed with unique information

The antenna emits radio signals to activate a tag and read and write data to it. Antennas are the conduits between the tag and the transceiver, which controls the system's data acquisition and communication. The Transponder (*Transmitter – Responder*) is a device used

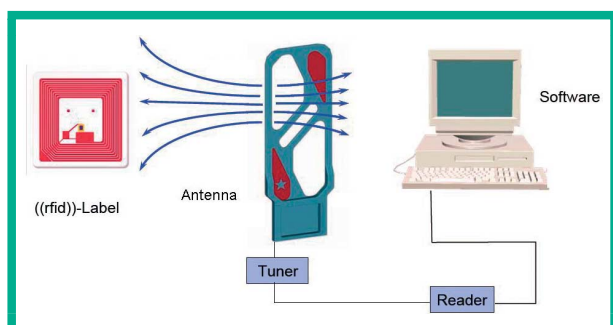


Fig. 1: Read/write data flows between RFID tag and host system.

for wireless transmission of identification codes. There are active / passive / semi-active RFID tags.

- Active tags require the use of some internal power source or battery.
- Passive tags do not require an internal power source or battery. The power required to activate the tag is drawn from the magnetic field created by the RFID reader. Tags described in this report are passive ones.
- Semi-active tags require power to work the circuitry of the chip but still communicate RF passively.

2.2. General applications

The basic principle of RFID is very old and was used already during World War II for identification of military aircrafts sending a unique identifier on radio frequencies. Further technological advances in electronics let devices become smaller and smaller such that nowadays these devices can be integrated into labels and thus making "smart" labels of them.

The application as such is already widely used in different areas of daily life. Most people are using it already without being aware of using hightech. Radio keys for cars are based on this technology, it is used for commercial laundry services, toll collect systems on highways (we.g. Bundesautobahnen in Germany), in library systems and will be used for ticketing and visitor's identification (via wrist bands) during next soccer/football World Championship in Germany 2006.

Very promising pilot concepts for retail applications have been implemented by Wal-Mart (USA), Metro (Future Store, Rheinsberg, Germany) and Migros (Smart Store, Zürich-Regensdorf, Switzerland). Unfortunately, however, these pilot installations have suffered from unfavourable reportings in media, suggesting violation of personal data protection by use of this technology.

Surprisingly no objections came up when decisions after 9–11 (destruction of World Trade Center in New York) were made to include RFIDs containing biometrical data (like electronic fingerprints) in passports. New German passports will contain RFID from late 2005.

This is already current practice with the European animal passport for movement of cats and dogs across European borders since October 2004. In this applica-



Fig. 2: European Pet Passport as example for daily-use RFID application.

tion, however, RFID tags are inserted beneath the skin in the cat's or dog's shoulder (Fig. 2).

Military applications (first launched by the US Department of Defense) were recently used for logistics in Iraq War for tracking thousands of containers daily, where normal bar code labels could have been used as well, but are not resistant enough against heat, moisture, mechanical stress and other challenging environmental impacts. US Military has the world's largest active RFID logistics tracking system, to monitor and manage 270 000 cargo containers transporting military supplies throughout 400 locations in more than 40 countries.

In May 2005 a contract was awarded to a company in California for a system used in a jail, which continuously locates and tracks inmate and officer movements by means of RFID and will be evaluated to measure its effectiveness in reducing and resolving violent incidents and impacting operating costs.

Applications in health care include "VeriChip" [1], a system recently approved by FDA and based on a subcutaneously applied RFID in humans, preventing dosing and medication errors in hospitals by real-time linking of patient data with medication schemes or matching blood samples to patients with wrist bands in order to enhance blood transfusion safety.

2.3. Functional details of current RFID tags suitable for use in the pharmaceutical industry

Most RFID tags used in the pharmaceutical industry are assembled in labels as inlets between glue and paper. The microchip is attached to an antenna that receives signals from and sends signals to a reader. The tag contains a unique serial number (i.e. no 2 tags are the same). Additional data storage is available to further identify the tagged item. The tags come in many different sizes and shapes (Fig. 3).

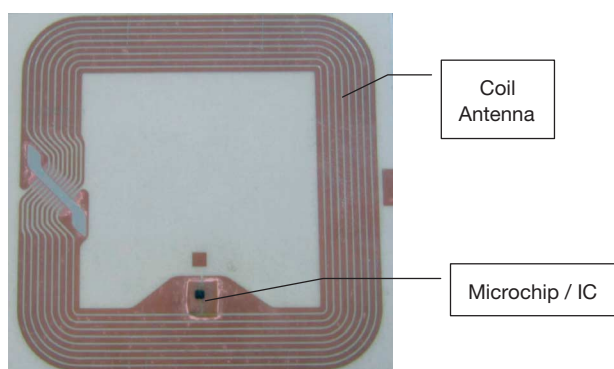


Fig. 3: Coil antenna with RFID microchip/tag.

Advantages of this technology integrated in labels for pharmaceutical use are to be seen as follows:

- No need for line-of-sight interrogation (i.e. data are readable through closed cartons and through a variety of substances such as snow, fog, ice, paint, crusted grime, and other visually and environmentally challenging conditions, where barcodes or other optically read technologies would be useless)
- simultaneous identification (not sequential as with barcodes)
- no space requirements on labels in contrast to barcodes since the tag is in the label
- “double layer information” on the label (open readable text and stored information on the tag not publicly accessible)
- difficult to duplicate
- RFID tags can also be read at remarkable speeds, in most cases responding in less than 100 milliseconds

These advantages are to be balanced against common *disadvantages* of this technology as follows:

- Reading distance is limited (depending on type of tag and radio frequency)
- Reliability of bulk readings is still to be improved but can be managed by adjustments in packaging design (e.g. orientation of tags within the pack) and processes
- Some substrates for the labels (liquids as in small and large volume parenterals and metals like MDI [metered dose inhaler], canisters or blister foils) require extra measures to overcome physical hurdles
- Costs (currently 0,3–0,7 € per tag)

The reader and encoder hardware market is rapidly evolving.

Readers can be obtained as handhelds (e.g. Compact Flash Cards integrated in current PDAs) or stationary readers/encoders integrated in packaging/printing lines or warehouse installations, Fig. 4).



Fig. 4: Pocket PC with integrated RFID read/write compact flash card.

3. Drivers, hurdles and current status of implementation in pharmaceutical industry

Current reluctance in the pharmaceutical industry to invest more capacity into implementation of RFID technology suggests to consider RFID to be a hype rather than reality.

3.1. Regulatory situation

However, recent FDA initiatives targeting on anti-counterfeiting of drugs will force the global industry to react.

The FDA's Counterfeit Drug Task Force issued a final report in February 2004 [2] urging drugmakers to adopt electronic track-and-trace technology and other authentication tools by 2007 “Radio-frequency identification (RFID) tagging of products by manufacturers, wholesalers and retailers appears to be the most promising approach to reliable product tracking and tracing”, the report concluded [3].

Since industry claimed to be prevented from rapid implementation of RFID by current GMP regulations, the FDA took the initiative to encourage industry for respective investments and published a Compliance Policy Guide [4] (CPG).

The CPG describes the FDA's intent to exercise enforcement discretion until December 31, 2007 concerning certain regulatory requirements to facilitate the performance of feasibility studies and pilot programs involving RFID tags for drugs.

Published concerns about applicability of 21 CFR Part 11 (electronic records / electronic signatures) restrictions to RFID [5] seem to be resolvable.

From the regulatory point of view the FDA as a hurdle is thus no excuse any more.

3.2. Strategy and infrastructure issues

However, based on author's experience from contacts within industry mostly the very basics necessary for implementation are not known, i.e., homeworks have not yet been completed (or at least not published).

The visionary "Real World Awareness" of items within supply chain operations can only be achieved if and when business objectives for relevant operations have been defined and RFID can be integrated into industry's business processes and strategies.

This requires to build up a respective RFID business case as a first step in understanding how this technology can develop high performance results. This should normally comprise considerations like

- data gathering and analysis,
- developing and challenging a hypothesis,
- examining current technical architecture (including existing IT systems),
- executing cost benefit calculations,
- evaluating the opportunities and finding the value,
- constructing an implementation plan.

The need for RFID has to come out of the (thoroughly investigated, mapped and realistic) processes rather than from the technology as such currently being *en vogue* and only seen as *nice to have*.

In order to harvest from the opportunities like tracking of work in progress and real time location of items offered by the technology industry has to invest into analysis of processes before.

Problems in managing the complexity of these processes have led to a lot of publications on the "what's" and "if's" and "should's" [6–8] but very few about practical experience and implementation problems or benefits.

According to a study performed by Accenture [9] "pharmaceutical manufacturers are looking to deploy the technology on the item level" mainly in order to retrieve the drug pedigree down to the item level.

Electronics Industry (Philips Semiconductors, TAG-SYS, Texas Instruments Inc.) immediately responded with a White Paper [10] "Item-level Visibility in the Pharmaceutical Supply Chain: A Comparison of HF and UHF Technologies" in July 2004 to demonstrate technological feasibility and applicability of RFID according to pharmaceutical industry's needs. This, however, requires this industry's readiness to adapt drug packs and packing processes.

Business/packaging processes may be adjusted after thorough investigation but changes in drug packs (especially on the primary packaging level like blisters or bottles) may require prior approval of authorities (e.g. FDA) based on new stability data, which at the end of the day delays the implementation efforts if not started early.

However, very few pharmaceutical manufacturers have shown readiness to adjust their processes and packagings so far.

Most just try to add RFID tags to their materials (like cartons or labels) rather than adjusting their infrastructure as necessary and then fail.

3.3. Technological and harmonisation issues

Passive as well as active RFID tags contain a unique Serialized Global Trade Item Number (SGTIN) encoded to the tag during tag manufacture. This process is known as "Mass Serialization".

The idea behind this was to enable globally clear identification of items containing a tag and was developed by the MIT. In the meantime global further development was transferred to an industry consortium called EPCglobal (EPC = Electronic Product Code).

However, standardisation issues for EPC have not yet been fully resolved and may exhibit a hurdle for the next 1–2 years.

A similar situation is to be faced with radio frequencies used for RFID purposes.

Since reading distances can be tackled with via different frequencies and different ERPs (Effective Radiative Power; currently 0.5 and 2 W at UHF) standardisation of frequencies and ERPs is still an issue.

Whereas tags and reading/encoding hardware for high frequency (HF) 13.56 MHz band is well established, industry is also seeking for implementation of Ultra High Frequency (UHF; 868 MHz) tags, since reading distance can be higher in these cases. Some industries consider mixed application of both technologies (HF and UHF), resulting in complex hardware and IT solutions.

3.4. Potential threats for pharmaceutical industry

Concerns have been reported that data stored on RFID tags might be subject to data theft and subsequent counterfeiting. The EPCglobal initiative is actively working on this issue. Since the unique global identifier is unerasably encoded to each single tag, coupling of this information together with company specific coding may ensure that both codes together become unique. Thus the remaining question is whether the SGTIN (see above) can be replaced on single tags. Since the pharmaceutical industry strives to apply RFIDs on the item level, such a fraud would mean to change each tag on any item which is a huge effort with a questionable effect.

We see threats more in insufficient adjustments of processes and packaging designs, since orientation of the tag towards the reader's antenna may impact the reading results and thus the supply visibility in its entirety. If 100 % pulk reading¹⁾ results cannot be achieved, the vision of fully tracking and tracing the supply chain down to the patient may not work and thus investments are voided.

¹⁾ "Pulk reading" means simultaneous recognition of data on more than one item.

Investments may be voided, too, if the pharmaceutical industry will not agree to a common standard of tags and data structures stored on the tags. If such an agreement cannot be achieved in time authorities could force industry to respective standards. Thus the preferable solution should be a pro-active approach of industry rather than waiting for more regulation by authorities.

The threats discussed here, however, do not apply to implementation of RFID in clinical supply chain as discussed below. Clinical supply chain is thus offering a unique opportunity for pioneering RFID application in Pharmaceutical Industry.

4. Background and strategy of implementation in Altana Pharma's clinical supply chain

Having mapped our business processes and workflows already some time ago, we have been in the unique position to clearly identify the opportunities of RFID application for achieving quick wins very rapidly. First contacts with technology providers were established during the world's biggest packaging fair Interpack in Düsseldorf (Germany) in 2002 already.

Being strongly focussed on time to clinic and time to market, we have been continuously looking for opportunities to shorten cycle times wherever possible. This led to a premium position in this regard in pharmaceutical industry (as proven by respective benchmarks).

Our Strategic Proposition as compared to the implementation of RFID with commercial pharmaceutical products is that cost constraints given there when calculating COGS (Cost of Goods Sold), do not apply in the respective extent to clinical material. Benchmarks have shown that the expenditures for clinical material on average amount only to 5–8 % of the total costs spent for a clinical study.

As long as time to clinic can be improved by such an approach the financial opportunities gained in this field exhibit much larger savings as compared to the costs for implementation and procurement of tags and hardware. This is why in clinical supply chain targets differ from commercial supply chain: it is 100 % quality on the item (patient) level and cycle time that pays.

Most of the other disadvantages listed above do not apply with clinical supply chain either:

- Violation of personal data protection requirements is not an issue since no personal data (e.g. of patients involved in clinical trials) are stored on the tag
- Standardisation of globally unique tag identifiers is not an issue since own numerically coded identifiers will be coded on the tag for later retrieval
- Falsification of this code is not an issue since no third party knows the syntax behind the code and the information is of no interest to anyone not involved in the trial logistics

- Frequency band harmonisation is not an issue since the requirement for 100 % bulk reading results requires 13.56 MHz and this is officially accepted as standard in US as well
- Harmonisation of requirements with other companies in industry for tags or coding is not an issue since it is undesired: we do not want other companies to read our tags
- Clinical supplies are “built to order” which (in contrast to commercial drugs) enables us to adapt packs and packaging processes to the particular needs of RFID application

Based upon these considerations clinical supply chain provides an ideal starting position for implementation of RFID and all of the advantages can be made use of in this typical “built to order” process.

Since some technical basics are to be clarified prior to first application of RFID technology our implementation strategy reads as “think big, start smart”. This is why we started off with a pilot project called SIMPL (Standardization of Investigational Medicinal Product Labels) as described below.

Quick wins are to be expected only when levers for improvements can be clearly identified within the business workflows and processes. We will get quick (at least as compared to current industry approaches to RFID) wins based on the pilot project (SIMPL), but the focus is on solid mid to long-term achievements of business objectives.

5. Strategy execution: The SIMPL project as pilot

Since RFID tags will be integrated in labels used for clinical material the SIMPL (Standardization of Investigational Medicinal Product Labels) project as a pilot is focussed on clinical supplies labels containing RFID chips, their respective design and materials and integration into the business and pharmaceutical processes.

Understanding the opportunities of RFID in the clinical supplies area needs some insight into the packaging details with clinical supplies.

Clinical supplies comprise a primary pack (like bottles, MDI canisters, blisters etc.) containing the drug. These primary packs are packed according to the patient/treatment randomisation scheme (following the requirements of the clinical study protocol) into cartons and these again into cartons and those again into cartons etc. resulting e.g. in patient packs, period packs, investigator packs, site shippers and so on. At the end a pack coming to distribution and shipment may contain a pack in the pack in the pack in the pack etc. (see Fig. 5) following a considerably complex packaging design.

This is looking similar to the Russian Matroschka puppet consisting of different “layers” of other Matroschkas in it (Fig. 6).

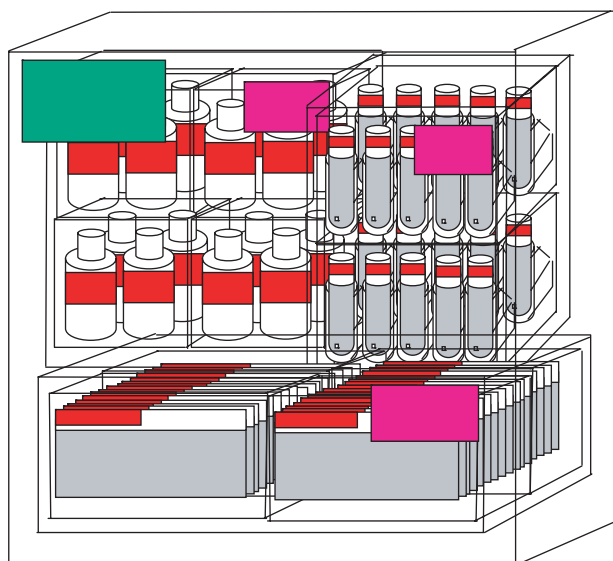


Fig. 5: Clinical Supply pack-in-the-pack principle.



Fig. 6: Illustration of Clinical Supplies pack-in-the-pack principle: Matroschka Puppet-in-the-Puppet.

Most of these packs from the different packaging levels are labelled with a seal for tamper proofing purposes. Majority of packaging and labelling operations are done manually since we deal with individualized medication in clinical trials.

Different to processes in commercial drug manufacture clinical supplies regulations request an additional final check for correct randomisation and blinding. Since most of the packs are sealed for tamper proofing purposes they cannot be opened to take a sample for analytical checking on correct blinding without destroying the pack. This requires currently a sampling process with replacement of the samples drawn. The statement made from the analytical results can only be given for the results of the sample but may not be representative for the entire packaging run.

This is why there is a strong interest not only to save the sampling process but to have 100 % (i.e. full batch) of all packs assessed on correct blinding and randomisation.

Since the labelling process is run manually it makes no difference whether the label applied on the carton contains a tag or not. In so far the labelling process as such does not have to be modified. During label printing process potential omission of the former barcode may save valuable text space on the label.

Once the RFID tag contained in the label (and thus identifying packaging steps and pack contents via the host database) is on the individual item, at the end of the day all of the tags can be read simultaneously without line-of-sight need (as with barcodes), real-time checked on plausibility against the database generated during electronic batch recording along the packaging and labelling process and a 100 % control of all packs is enabled.

Current GMP regulations (GMP Annex 17) allow for “parametric release” the basis of which is being provided by RFID in this case.

Based on these considerations this pilot application thus provides accomplishment of some of the strategic objectives within clinical supplies management:

- Higher (i.e. 100 %) assurance of correct blinding/randomisation
- Savings in time (by elimination of a final step in the series of processes)
- Savings by no waste of packs by sampling procedure and replacements
- Savings in (analytical) personal costs
- Online visibility of the entire packaging process
- Error tracking capabilities
- Savings in text space on the label (urgently needed for printing of text required by regulations)
- “Double-layer information” on the tagged label: readable (printed) text and non-readable information (contained as data in the encoded tag)

We succeeded in achieving efficiency gains by combining knowledge from packaging process, business process (known from former process mapping studies), analytical requirements and GMP requirements with IT and hardware know-how.

5.1. Investigating and resolving technical constraints

Since 100 % bulk reading result is an issue with the pilot application, decision was made to use 13.56 MHz tags only. This requires adjustments in packaging design to a bigger extent as compared with UHF tags but pays, because risk of double reads is lower and standardisation is not an issue any more.

The technical weakness of reading tags affixed on metallic cover foils commonly used for blisters does not allow to apply RFID tags directly on the blister. This can be overcome by placing blisters in sufficient distance within the carton and have RFID tags located accordingly with distance to metallic parts.

5.2. Harmonizing RFID requirements with label specs

A label containing a RFID tag normally comprises three layers:

1. The outer layer (often paper) where readable text is printed on. This printing is done individually for each patient with clinical supplies using high-speed thermotransfer printers taking patient variables dynamically from the host database.
2. The intermediate layer containing the tag and its antenna. Since the tag is thicker than the paper layer a small hill is formed on the paper's surface by the chip. In the area of this hill rolls of thermotransfer printers lift off the contact with paper and thus no printed text is applied in this area. There are two options available to overcome this:
 - a) Print first and bring layers together afterwards. This requires considerable investments in respective equipment and is not flexible enough in regard of sizes and formats used with clinical supplies.
 - b) Arrange chip at an appropriate location of the label and do not print on this area. This requires a specific design of the label but is cheaper on the long run and provides more flexibility in label design.

This shows that harmonisation between the different components of a layer must be accepted as well as modifications in packaging design in general.

5.3. People

Clinical supplies preparation is a highly complex and hightech business. This requires people to tackle with the numerous challenges also when no RFID is under consideration. This is why no additional resources are needed for implementation of RFID since the required combination of know-how is available any way and capacity is then a matter of priorities only.

Development of electronic issues and label hardware was outsourced and thus did not require internal resources.

Since the packaging and label application process remains unmodified RFID application does not cause additional resource needs in this area either.

6. Future perspectives

Once the technology is established based on the outcomes of the SIMPL project, we will extend the application to on-line track-and-trace of the packaging process, monitor clinical material warehouse stocks in real-time, enhance the visibility of the entire clinical supply chain by real-time location of items, comply with regulatory requirements for tracking the pedigree in regard of potential product recalls during clinical studies, and rationalising drug accountability ("pill-counting") at the end of the clinical study.

The vision on the long run is to achieve global and world wide (CS [Clinical Supplies] departments, local operating companies and investigational sites) inventory visibility of clinical supplies in real-time. This would help to further ensure regulatory compliance and enhance efficiency also in the GCP area. Opportunities offered by the RFID technology may be realized with low budget and comparably low resources – what is needed is: integral know-how about all associated processes and contexts.

7. Conclusion

The lessons learnt taught us to carefully monitor the market of new technologies in order to make careful considerations for potential applications in our business area.

This requires in-depth knowledge of own processes to make respective realistic assessments. Based on this knowledge and the outcome of our SIMPL pilot project we are optimistic to establish RFID successfully in the clinical supply chain and achieve, what the "think big"-approach suggests.

Acknowledgements

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