



RFID in Life Sciences Series: Part 3

RFID in Clinical Trials

Accelerating the Process

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The Learning Chain:

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Executive Summary



Since early times man has searched for life-saving compounds, and has found magical elixirs in the minerals, plants and animals he saw around himself. His more recent efforts include the creation of chemical combinations, matching the corresponding effects of those combinations with the symptoms he is hoping to cure.

Today, this process has been formalized, and is the fundamental purpose of the pharmaceutical industry, with collective eons and dollars resulting in drugs that extend and save lives.

The discovery of a 'block buster drug' brings rewards for manufacturers and investors alike.

WHY A REPORT ON THE USE OF RFID IN THE DISCOVERY PROCESS?

Estimates for the true cost of drug manufacturing, from drug discovery to commercialization, range from hundreds of millions to billions of dollars. Irrespective of the financial considerations, finding a cure and improving the quality of life for those suffering from disease has immeasurable value. This report shows that reducing the cost of developing drugs, from discovery to the marketplace, translates into a win for everyone in the Life Sciences supply chain.

Monitoring the complex and lengthy business processes, as well as capturing and disseminating critical data and information in a highly regulated industry are critical to the success of this industry. This report, the third in the series related to the use of advanced technology enablers in the Life Sciences Industry, explores using technology to streamline the entire business process. In particular, this report evaluates the use of wireless networks, coupled with auto-identification technologies – sensors, RFID and bar-codes – to identify both current levels of adoption as well as future areas of opportunity.

In addition, this report identifies some of the key constraints, as well as potential process improvements that could be supported by technology, enabling the industry to streamline the discovery, clinical trials, and commercialization processes – reducing both time to market and, optimistically, time to cure!

HOW THIS REPORT IS ORGANIZED

In this report, we have included survey responses from both the practitioners and the solution providers, as well as additional information that may be new to both. Our goal is to provide each constituency with a frame of reference that is relevant, while stimulating thought and innovation in the use of auto identification technology in the early stages of pharmaceutical discovery, clinical trials and ramp up to manufacturing.

We have broken this report into a review of each of the three major steps required in order to transform laboratory experiments into viable products, outlining within each step some of the key issues and areas of opportunity for technological solutions.

This report is addressed to two audiences:

| | |
|----------------------------------|---|
| <p>Practitioners</p> | <p>Enterprises engaged in the discovery and approval process for new pharmaceutical and life sciences products. This community is familiar with the processes and procedures that are necessary to take a new compound from 'potential wonder drug' to approved commercial product.</p> <p>The level of understanding of technology and solution components for the capture and dissemination of data by this community is limited.</p> |
| <p>Solution Providers</p> | <p>Enterprises that have products and services that can be used to manage and control the information gathered during the discovery and approval of new pharmaceutical and life sciences products.</p> <p>Their level of understanding of the issues, processes and procedures involved in the 'discovery and approval' process is limited. Their experience and expertise relates to the use and introduction of auto identification technology to manage information, streamline manual processes, and diffuse this across a diverse community.</p> |

Table 1 — Technology Expertise Levels



WHO SHOULD READ THIS REPORT

The material in this report is of interest to the following groups of people:

- Pharmaceutical and Biotech manufacturers — research and development personnel
- RFID Vendors — wireless technology providers across the medical spectrum
- Software/Solutions providers — companies across the medical spectrum
- Contract Research Organizations
- Suppliers — of goods and services to the Life Sciences Industry
- Government, Policy and Trade Associations



Major Challenges in the Discovery Process

Modern drug discovery has come a long way from the ‘sorcerer’s laboratory’ of the past.

Drug research explores the functioning of the body – both normal and abnormal – at the most basic levels. The fundamental question asked is “If this compound changes the functioning of the body in a positive manner, will this be a valuable compound?” The answer to this question leads to the concept of how the compound might be used to prevent, treat or cure a medical condition – the target for further drug research.

Research is a time-consuming process, with hundreds or even thousands of potential compounds and combinations being created and evaluated. Using a series of ‘test-tube’ laboratory experiments known as assays, a variety of compounds are laboriously added to enzymes, cell cultures and cellular substances. The objective is to find different combinations and additions that have a chemical effect. Improving the performance of the compound by changing the structure normally involves testing tens and even hundreds of different compounds and combinations. The total investment is staggering.

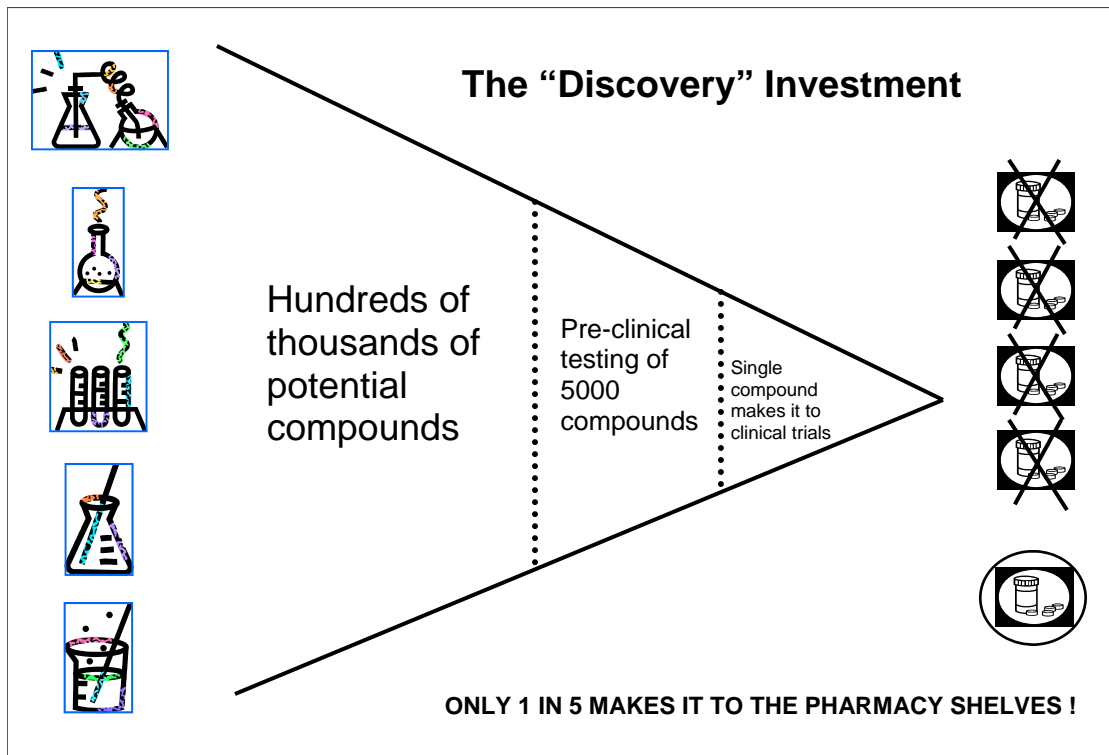


Figure 1 — The Discovery Investment

UNDERSTANDING THE DISCOVERY PROCESS

The 'Discovery' process is the first link in the complex 'supply chain' for the Life Sciences Industry. Activities taking place in these early days need to be monitored and recorded, ensuring that a blueprint is created to track the development of compounds in a consistent manner. Each of the steps taken in developing the 'exploratory compound' will need to be replicated in a production environment, thus transforming the promise of a cure into an economic reality.

WHY IT MATTERS - THE VALUE OF THE 'PIPELINE'

The Research and Development 'Pipeline' is key to stock valuation and shareholder value. The biotechnology leaders have a long-standing tradition of reinvesting a significant percentage of earned revenues back into research and development — a practice that has proven successful in transforming promising candidates into important new products. A robust and promising product pipeline assures the continued supply of new drugs as well as continued shareholder investment. (For a sample pipeline, see Addendum 2.)



TAKING THE WRONG ROAD

Not all research has a positive outcome, and more often than scientists like to think about, research has to be abandoned if a drug or compound is poorly absorbed, is unsafe or does not have the desired result. Pharmaceutical Research and Manufacturers of America estimates that only five in five thousand compounds that enter pre-clinical testing make it to human testing, and only one of those five may be safe and effective enough to reach pharmacy shelves. (As illustrated in figure 1, preceding page)

However, there are many interesting twists and turns on the road to discovery. In some cases, even though things do not look promising, the scientists persevere, discovering valuable compounds in the research work that may have been abandoned by others. There are documented cases where compounds have been 'shelved' due to lack of success on a spe-

cific disease, only to be re-activated and found to work well on another disease or medical condition. Another twist relates to the approval of a specific compound for one condition, only to discover that this compound is a potential cure for additional diseases. For example, a specific drug which is in Phase IV approval for one condition may also have begun the approval process for additional applications.

| DISCOVERY PROCESS | | | | | | | | |
|-------------------|--|--|--|--|---|--|--|--|
| Major Steps | 1—Discovery | | 2—Clinical Trials | | | | 3—Approval | |
| PROCESS STEP | Discovery Computer clues, mother nature, experimental compounds | Animal Testing | Phase 1 20 – 80 participants | Phase 2 100 – 300 participants | Phase 3 1000 – 3000 participants | Phase 4 Optimal use, dosage, storage and packaging | Approval | Manufacturing ramp up and general distribution |
| CONSTITUENTS | Manufacturer's scientists Suppliers of raw ingredients | OHRP, scientists and biologists, IRB.FDA | CRO OHRP IRB – doctors Nurses HHS FDA | CRO OHRP IRB – doctors Nurses HHS FDA | CRO OHRP IRB – doctors Nurses HHS FDA | CRO OHRP IRB – doctors Nurses HHS FDA | FDA/ Manufacturer Suppliers | Manufacturer and supply chain partners |
| DATA REQUIRED | Compounds and interactions | Interactions and results | Safety, Dosage, Side effects | Effectiveness and safety issues | Specific use, side effects, comparison with existing treatments | Optimal use and results – dosage, dispensing configuration, packaging and labeling | All info obtained during previous stages | All data related to Supply Make Store Ship |

Table 2 — The Discovery Process

Understanding the Major Steps in the Discovery Core Process

When evaluating the introduction of technology into a complex process it is necessary to have a clear understanding of all the major steps and procedures that need to be managed. The following is an overview of the core process, and the associated steps including the discovery, approval and market introduction of new Life Science products.

STEP 1 – DISCOVERING A CURE

Computer Simulation

Introducing computers to simulate an enzyme or other drug target – designing different chemical structures and evaluating the interaction – is one discovery technique. It is possible to create a representation of a receptor site, as well as a compound that would prevent an enzyme from attaching to this site. These ‘computer clues’ assist in creating potential new compounds and combinations of ingredients. However they do not provide any conclusive answers. Computer simulated ‘compound creation’ needs to be tested further in a biological system.



Working with ‘Mother Nature’

Building on more traditional medicine, an alternative approach includes testing compounds created naturally by microscopic organisms. Success has been achieved through experimentation with fungi, viruses, and molds, such as the discovery of penicillin and other antibiotics. The process includes growing these microorganisms in what is known as a ‘fermentation broth,’ with one type of organism per broth. This is a time- and labor-intensive process. In many cases, more than 100,000 broths are cultured and tested to establish whether any of the compounds has a desired effect on the target enzyme.

Animal Testing

The next stage, beyond the laboratory test tube environment, is to extend the test to a biological subject – a living animal. This is a contentious point, and drug companies make a conscious effort to use a limited number of animals at this stage, as well as ensure their humane care. It is common to use two or more species, as the drug/compound



may affect one species differently than another. The tests are designed to establish whether the drug has potential negative side effects, and what these effects are at varying dosage levels. Tests done with animal subjects form the baseline for testing with humans, as well as creating the initial data requirements for product labeling – important much later on in the process. Up until this point, the research has aimed at discovering what a drug does to the body. Now, it is important to find out what the body does to the drug. So, in animal testing, scientists measure how much of a drug is absorbed into the blood, how it is broken down chemically in the body, the toxicity of its breakdown products (metabolites), and how quickly the drug and its metabolites are excreted from the body. Sometimes, such tests find a metabolite that is more effective than the drug originally picked for development. This can be an exciting moment – discovering a metabolite that holds the promise for a miracle cure not previously anticipated!

STEP 2 - CLINICAL TRIALS



The development of new drugs and compounds is conducted by research and development organizations, that gather detailed information related to each of the critical processes outlined above. These results are carefully documented and submitted for review by FDA physicians, scientists, and other staff members. Based on the information reviewed, the FDA determines whether the drug is safe enough to test in humans, in what are known as Clinical Trials. Clinical

trials are conducted in phases, each of which has a different objective, and enables scientists to answer specific questions and address different potential issues and concerns.

Phase I

The experimental drug or treatment is tested for the first time in a small group of human subjects (20-80) to evaluate the safety, determine a safe dosage range, and identify side effects.

Phase II

The experimental study drug or treatment is given to a larger group of people (100-300) in order to establish effectiveness and identify potential safety issues.

Phase III

The experimental compound, drug or treatment is evaluated using a much larger group of subjects (1,000-3,000). This assists in identifying effectiveness as a treatment for specific conditions, identifying and monitoring potential side effects, and ensuring that the drug is safe for human consumption. In addition, the drug/treatment is evaluated in comparison to pre-existing treatments.

Phase IV

Assuming that no adverse effects have been identified, and the drug/treatment offers positive benefits, this stage in the process is used to obtain additional information related to optimal use, as well as preferred packaging, labeling and storage guidelines.

STEP 3 – APPROVAL FOR COMMERCIALIZATION

Clinical Trials include the most important steps in the discovery and development process – ensuring that patient safety is not compromised through the promise of a cure. As is apparent, this is a time-consuming and data-intensive process. Consistent with ‘cost avoidance’ this is an area frequently outsourced to Contract Research Organizations (CROs) – adding another link into an already complex chain. Unlike ‘mainstream’ manufacturing and distribution environments, where information technology is the norm, the clinical trials process relies to a large extent on human data capture, data entry into management systems and manual recording and control. These processes and procedures are prone to errors and inefficiencies – providing an area of opportunity for information management technology.



Playing by the Rule Book

Most clinical trials in the United States are federally regulated with built-in safeguards to protect participants. Today, the Office for Human Research Protections (OHRP) in the Department of Health and Human Services (HHS) leads the department's programs for the protection of human research participants, and oversees human protection in HHS-funded research

Role of the FDA

The FDA has authority over the clinical trials process, for pharmaceutical, biologic and medical device products that are regulated by the agency. This authority includes studies that are HHS-funded (with joint oversight by the FDA and the OHRP), as well as studies that are solely funded by industry or by private parties. Many clinical trials are not subject to FDA regulation but are monitored by the institution sponsoring the trial, such as a hospital. In addition to having authority over certain clinical trials, the FDA has final approval over which products will be approved for public use. This authority includes prescribing how the product should be packaged, what information should be included in the label, such as directions for use, storage requirements, side effects and other warnings.

Institutional Review Board

The institutional review board (IRB) comprises health care professionals from the institution where the clinical trial takes place, as well as members of the local community. The board oversees the clinical trial process and scrutinizes all trial activities including recruitment, advertising, and potential risks. The IRB also ensures that FDA regulations are followed in a particular clinical trial.

Protocols

Clinical trials follow written procedures – or protocols – that define each of the steps to be taken when conducting a controlled study. This ensures that the appropriate and valid data is captured throughout the clinical trial process.

"Expanded access" protocol

In certain cases some patients do not qualify for participation in standard clinical trials due to health, age or other factors. In these cases, assuming that these patients could potentially benefit from the use of this experimental drug/treatment the FDA regulations allow for the 'expanded access' use and evaluation of the drug. An example of this is a [treatment IND](#) (Investigational New Drug application) or treatment protocol. This is a relatively unrestricted study where the intent is to evaluate the drug/treatment using subjects who have a potentially terminal disease for which there is no known cure. An additional objective of the treatment IND/protocol is to generate additional data related to the safety and potential side effects of the drug. These 'expanded access' protocols are only allowed where clinical practitioners are investigating the result of treatment in well-controlled studies or where all other studies and approaches have been applied. A further condition is that the drug has potential positive results for patients that will be involved in this study under this protocol. Studies cannot present unreasonable risks to the patients participating in the study.

How are participants protected during a clinical trial?

Today, (in the USA) the Office for Human Research Protections (OHRP) in the Department of Health and Human Services (HHS) leads the department's programs for the protection of human research participants, and oversees human protection in HHS-funded research. Most clinical trials are federally regulated with built-in safeguards to protect participants. The FDA inspects clinical study sites and investigates all participants engaged in the research and evaluation of the effects of experimental drugs/treatments. The combination of FDA, Institutional Review boards and appropriate government agencies, ensures that the welfare, rights and safety of participants are safeguarded.

US Food and Drug Administration

<http://www.fda.gov/fdac/special/testtubetopatient/default.htm>



RFID Auto-Identification in the Clinical Trials Process

CONCEPTUAL VIEW

All parties engaged in the discovery and clinical trials process need access to detailed data and information. Having this available in a single 'system of record' or 'single version of the truth' (SVOT) would facilitate timely and accurate data capture and sharing, reducing time to market – and to cure!

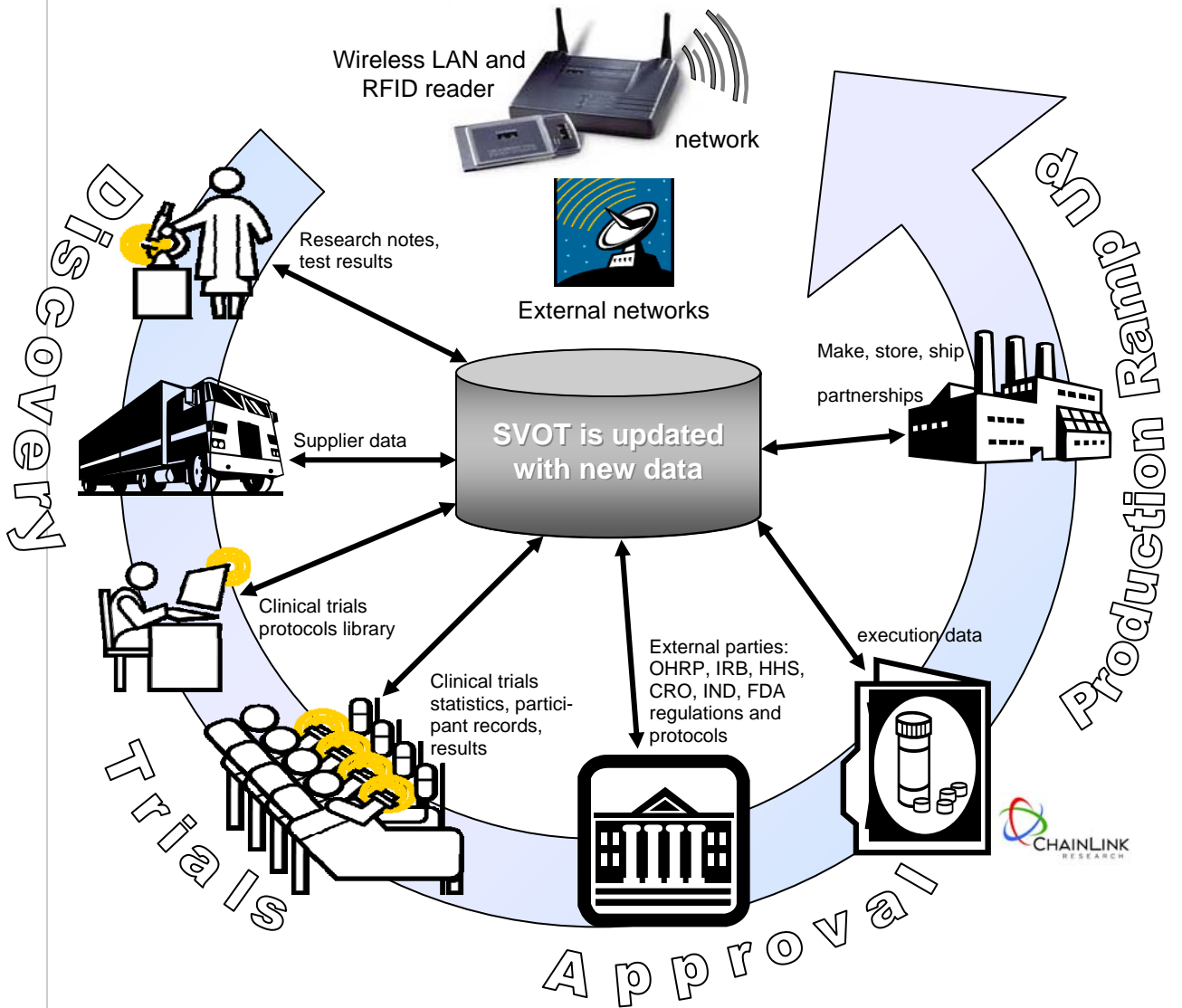


Figure 2 — RFID in Clinical Trials Conceptual View

THE PROMISE VERSUS REALITY

Several sectors of the Life Sciences industry have already adopted technology enablers to manage and monitor the movement of goods and information (for example the use of RFID for chain of custody control and e-Pedigree). Based on interviews with a variety of constituents in the 'early days' of discovery and approval, it became apparent that adoption of these technologies by this sector is limited at best. Several areas of constraint and future opportunity were identified, and include:

Supplier Selection and Management

This continues to provide challenges, especially when there are single sources of supply for specific source ingredients. Visibility and access to exception level data would be valuable in the following areas:

- Material tracking - inbound and throughout each process
- Chain of custody within the total process
- Testing and results - detailed tracking and supplier/product/results integration



Clinical Trials Data Management

In view of the large number of participants, and the level of detail/volume of data required, any technology that could assist in the following areas was considered of extreme benefit:

- Identification of placebo versus active products
- Tracking of all steps when samples are sent to a clinical trial agency
- Tracking results and making associations to product/patient



POTENTIAL BENEFITS OF RFID AND SENSORS IN CLINICAL TRIALS

The research and discovery of new drugs and treatments involves many participants. In addition, a large amount of very detailed and granular data are captured and shared with all participants. This information is critical and forms the framework for developing commercially viable compounds, and packaging them in configurations that will ensure their purity and efficacy, from manufacturing to consumption. When taking the next step in the process – moving from the laboratory to the clinical trials environment – it is equally important to ensure that the data trail is detailed and controlled. This includes data related to packaging, storage, transportation and other factors that could impact the ‘state’ of the compounds that are being evaluated.

This is compounded by the increasing globalization of manufacturing operations, requiring a data source that enables participants to evaluate the impact of the environment on raw materials and finished products. According to the Biotechnology Industry Organization, there are currently 350 new biotech products in clinical trials, of which at least one-third are temperature-sensitive. As such, they need to be managed and monitored to ensure that they are not compromised by exposure to variations in temperature. This extreme element of supply chain management is known as ‘cold chain.’¹

Even for products that have no ‘cold chain’ requirements, the logistics process is an area of concern for clinical trials practitioners. Increased outsourcing of the clinical trials process to CROs – in many cases located in disparate geographic locations – has increased the number of players and steps in a complicated process. Concerns included the ability to control and monitor the movement of samples from source location to clinical environment – changes to the product either in transit or at rest could invalidate results. Packaging and labeling was an area of concern – as well as providing opportunities for the introduction of auto identification technology to monitor and control each link in the extended chain. In common with pharmaceutical manufacturing and distribution, the issue of chain of custody (aka e-pedigree) was one that was prone to ‘black holes’ and lack of consistent data. Responses to the survey confirmed that the introduction of RFID, sensors and other auto-identification technology would assist in monitoring and gathering data in both clinical trials and the manufacturing ramp up process.



1. See Report: *Cold Chains are Hot—Mastering the challenges of Temperature*
www.chainlinkresearch.com/research/detail.cfm?guid=49189262-B102-0E02-9EAC-24A8B4B3F899

How RFID could be used to improve the clinical trials process

The introduction of auto-identification technologies – in particular RFID and sensors – would facilitate the capture of digital data related to the specific location and state of materials, at the unique item level. It would also enable the tracking of placebo versus active compounds, with the immediate correlation between item and patient/subject. This data, in digital format, could be integrated into existing information systems, creating a ‘single system of record’ in critical data that could be shared by all participants. (See table 3, page 17)

How would it actually be used and how would the process change?

One of the biggest challenges in Clinical Trials is ensuring the efficacy of the compound as it moves from point of manufacture to point of consumption in the test environment. In addition, there is concern that the subjects consume the compound in the correct dosage level, at the correct time intervals. RFID/sensor tags could be applied to external packaging of raw materials and finished compounds. As they are moved through the ‘chain of custody’, all activities could be recorded, linked to the specific incidence of the item, ensuring that the compound has not been compromised due to environmental factors. The key activities at each point in the process could be monitored and recorded – for example, using RFID and

sensor technology in unit level packaging to record the time and date each patient consumed the test compound.

The data captured would create a digital audit trail, less prone to human error than the current process that includes manual data capture and secondary entry into information systems.



Challenges to using RFID

When introducing technology enablers, there is a level of distrust at the user level, including privacy concerns, the impact of technology on human tissues, interference with other electronic components, and general concerns related to the reliability of the data capture mechanism.

Issues that would need to be overcome

As with all changes to the status quo, there are both emotional and technical issues that need to be addressed. A change management program would be needed to ensure training for personnel and patients to comply with the new technology parameters. In addition, a technical evaluation would be needed to ensure that there are no technical barriers to implementation. One of the key technical considerations is the need to capture data across a diverse environment – taking into account the best technology components required in order to create an integrated flow of data across both ‘open’ and ‘closed’ loop environments. Key considerations include the evaluation of the appropriate frequency for the tags and readers that are implemented as part of a solution – see below for alternatives.



There are three frequency bands of RFID technology that could be used in a clinical environment:

- *Low Frequency (LF) tags are expensive and bulky, which makes them difficult to implement on a syringe.*
- *Ultra High Frequency (UHF) technology is relatively new. Global standards have yet to be defined. In addition, attenuation of the RF signal in fluids is greater than that of LF and HF RFID.*
- *High Frequency (HF) technology offers global standards, data security, good propagation through liquids, and is very prevalent and proven in a clinical environment.*

Success at Last

A recent example of the twists and turns involved in the discovery process is illustrated by the potential 'miracle drug' Tykerb. In mid September 2006, GlaxoSmithKline applied for regulatory approval for commercial release of the compound. This is a major milestone in a 17-year journey, in which multiple scientists have contributed to the success of the compound. Initial research and development on the compound began in 1989, when scientists at Burroughs Wellcome began investigational research, seeking a cure for cancer. When the company merged with Glaxo in 1995, the experimental compound was one of many that joined the pipeline of 'promising chemicals' and the research team was expanded to include scientists from Glaxo.

More years passed and time began to run out for the team of scientists working on the compound in the search for a cure for HER2 tumors (a common type of breast cancer). In 1997 the team in the UK was given one more year in which to complete their research and come up with a successful compound. They failed and the company decided to terminate research activities – until one of the oncology researchers in the Research Triangle Park, North Carolina, facility stepped in. He and a colleague traveled to the UK research facility for a week of fact-finding, returning to the US with literally hundreds of pages of laboratory results. The US team of chemists and biologists worked furiously, creating and screening hundreds of different chemicals, searching for the miracle ingredient that would kill the cancer and not harm the patient.

They were not alone in their quest – teams of scientists at rival drug companies were searching for the same cure. Glaxo Wellcome had made the most progress and applied for a patent for their cure. However, they had to complete the patent application in 1998, identifying a chemical and its specific mechanism of action. Failure to do so would negate their advantage and open the door for other teams with competing research. Literally, at the eleventh hour, a team of biologists 'cracked the code' and discovered GW572016, a chemical known as lapatinib ditosylate. This chemical kills HER2 positive tumor cells, and is the active ingredient in Tykerb.

Clinical trials commenced in 2001, studies showing that Tykerb, available in tablet form, had fewer side effects than the only other available treatment for the condition, Herceptin, an intravenous treatment for breast cancer. Taken in conjunction with Xeloda, an oral chemotherapy, the drug has been successful in treatment of women with breast cancer, arresting the development of tumors for over 8 months – versus alternative treatments that stop tumor growth for up to 4.5 months.

This success resulted in GSK cutting the trial short and making the drug available to all 324 participating woman suffering from breast cancer – while preparing their application to the FDA for marketing and distribution of the drug.

On March 13, 2007, the FDA granted approval to Tykerb® for use in combination with [capecitabine](#) (Xeloda®) for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress [HER2](#) (ErbB2) and who have received prior therapy including an [anthracycline](#), a [taxane](#), and [trastuzumab](#) (Herceptin®).

WHO IS REALLY USING RFID IN THE CLINICAL TRIALS ENVIRONMENT?

Survey responses revealed differing views in terms of the potential benefits of incorporating RFID into the Clinical Trials process. This is summarized in the following table:

| Areas of Benefit During Clinical Trials Process | RFID/Sensors Extremely Valuable | RFID/Sensors Moderately Valuable | RFID/Sensors Little or No Value | Don't Know |
|---|---------------------------------------|--|---------------------------------------|------------|
| Batch and lot number control | 40.0% | 26.7% | 10.0% | 23.3% |
| Monitoring state of products – temperature and other variants | 36.7% | 26.7% | 6.7% | 30.0% |
| Shipment of samples to CRO | 33.3% | 33.3% | 6.7% | 26.7% |
| Monitoring the administration and handling of compounds in CRO at the personnel level | 26.7% | 26.7% | 20.0% | 26.7% |
| Monitoring the dispensing of placebo versus active com- pounds and matching/tracking the correlation of dispensed drugs/placebos to patients' outcomes | 43.3% | 16.7% | 13.3% | 26.7% |
| Monitoring the actual consump- tion of compounds at the pa- tient/subject level (i.e. tracking time, quantity of product in- gested by subject) | 43.3% | 26.7% | 10.0% | 20.0% |
| Gathering data for submission to Institutional Review Board/ FDA approval | 26.7% | 23.3% | 26.7% | 23.3% |
| Monitoring chain of custody | 36.7% | 26.7% | 10.0% | 26.7% |
| Anti-tampering – alarms and alerts | 33.3% | 20.0% | 23.3% | 23.3% |
| Transportation – inbound & outbound | 36.7% | 26.7% | 13.3% | 23.3% |
| Storage – raw materials, labora- tory, samples | 26.7% | 23.3% | 20.0% | 30.0% |

Table 3 — Use of RFID in Clinical Trials

ORCHESTRATING THE CLINICAL TRIALS PROCESS

As expected, the majority of comments and concerns expressed by respondents to the survey related to consistency at the process level. Process Analytical Technology (PAT) is a recurring theme in pharmaceutical production – creating and sustaining the desired process steps in clinical trials requires the same level of data capture and analysis. Expressed in different ways, each of the respondents had frustrations related to the lack of data sharing across the ‘end to end’ process. Having more information related to pre-clinical testing – to include product storage and control – was one of the many areas of opportunity. Others include:

- **Process standards**—Lack of standards for process and control
- **Collection**—Paper based systems – need to manage and collate all responses
- **Horizontal data integration**—Record keeping – database incompatibility
- **International data integration**—International issues – methodology and data control
- **Accessibility**—Data accessibility and availability
- **Cost control**—Cost of Clinical Trials process – many players and many steps



For data captured during the clinical trials process in legacy systems, integration is a major requirement, as is shown by the following responses, which reflect the myriad of business processes (with their functional information systems) that are interdependent.

| What information systems does data captured during clinical trials need to be integrated into | Percent |
|---|---------|
| Laboratory Information Systems | 25.0% |
| Clinical Trial Information Management Systems | 37.5% |
| Transportation Information Systems | 15.6% |
| Warehouse Management Systems | 37.5% |
| Manufacturing Information Systems (MES, APS, etc.) | 28.1% |
| Packaging Information Systems | 18.8% |
| Other | 21.9% |

Table 4 — Application System Interface Requirements



PRE-MARKETING AND RAMP UP TO PRODUCTION

Once a product has passed the various levels of clinical trials, the race is on to bring it to market. Patent protection – a key to recovering the investments to date – is governed by a timeline. Streamlining the ramp up to production, in order to meet product volumes required for sampling and dispensing at a commercial level, would have both altruistic and financial benefits.

Issues of greatest concern related to the ramp up to commercial production involved several challenges in the area of supply chain management. In most pharmaceutical manufacturing environments, ensuring a consistent and reliable source of raw materials and components is a challenge. Single-sourcing for certain chemicals and starting materials adds weeks and months to production cycle time – and these are relatively mature supplier relationships. Finding suppliers for critical ingredients in the discovery process is one of many challenges which becomes greater once volume requirements for commercialization increase.

How RFID could be used to improve the process

The key issues in the ramp up to production include many of the same challenges that are being addressed by including RFID in the more formal pharmaceutical manufacturing process. Including RFID tags and sensors at the unit, package and pallet level facilitates the monitoring and control of starting ingredients and compounds as they move from supplier through production and packaging. The digital audit trail creates the key data for e-pedigree applications, ensuring product efficacy as well as reducing the opportunity for diversion and counterfeiting.

How would it actually be used and how would the process change

RFID tags and sensors could be applied to unit level packaging at the supplier location. The combination of RFID tags, readers and related network technology could create an environment in which it is possible to have a real time 'view' of the movement of product through the chain of custody. The inclusion of sensor technology would alert participants to changes in the compound, based on heat, humidity and other environmental factors. The addition of 'event based alerting mechanisms' would create an automated environment where deviations from plan could be identified in 'virtual real time' – potentially averting supply shortages or product quality issues. This is very different from the current process that is reliant on human readable packaging and handling.

Challenges to using RFID

In common with the introduction of RFID and sensor technology into a Clinical Trials environment, the challenges are both philosophical and technical. However, as the 'ramp up to production' includes many external parties – suppliers, carriers, storage providers etc. – the implementation of this technology would need to take into account capabilities and constraints across an extended community.

Issues that would need to be overcome

As highlighted earlier in this report, the clinical trials and pharmaceutical manufacturing is taking place in a truly global environment. As such, global standards for data capture and exchange need to be taken into account across a diverse geographic horizon. It is necessary to take into account the technical and other capabilities of all players involved in the

end-to-end chain of custody. In some cases it will be necessary to introduce ‘work around’ strategies and processes in order to ensure that data is captured in a seamless manner. Any implementation plan should include a detailed capabilities assessment, taking into account all participants. In common with EDI implementations in the past, any technology solution is only as strong as the weakest link!

Interviews and responses to the survey revealed many areas of benefit for the inclusion of RFID and sensors in the ‘ramp up’ to production. This is summarized in the following chart:

| Benefit during Ramp Up to production and commercialization | RFID/ Sensors Extremely Valuable | RFID/ Sensors Moderately Valuable | RFID/ Sensors Little or No Value | Don't Know |
|--|----------------------------------|-----------------------------------|----------------------------------|------------|
| Monitoring the adherence to the prescribed manufacturing process and procedure | 31.6% | 42.1% | 10.5% | 15.8% |
| Quality control (testing, sampling, etc.) | 42.1% | 42.1% | 5.3% | 10.5% |
| Batch and lot tracking | 42.1% | 31.6% | 10.5% | 15.8% |
| Tracking - visibility of location of inbound compounds | 42.1% | 26.3% | 21.1% | 10.5% |
| Tracing – having detailed trail of milestones and events for each shipment | 42.1% | 36.8% | 10.5% | 10.5% |
| Anti-tampering – alarms and alerts | 42.1% | 26.3% | 21.1% | 10.5% |
| Monitoring state of products – temperature and other variables | 52.6% | 21.1% | 10.5% | 15.8% |
| Monitoring chain of custody | 57.9% | 21.1% | 10.5% | 10.5% |
| Transportation – inbound & outbound | 47.4% | 26.3% | 15.8% | 10.5% |
| Storage – raw materials, WIP, finished goods, samples | 31.6% | 47.4% | 5.3% | 15.8% |

Table 5 — RFID Benefits

Practitioner technology adoption

Although the need for more granular data and the potential benefit of auto-identification technologies was acknowledged by most respondents, the adoption of these technologies appears to be relatively limited at present, as reflected in the responses from the practitioner community:

| Adoption of RFID and sensor technology | Already deployed (pilot or production) | Deploy during 2006-2007 | Deploy during 2008 or beyond | No plans to deploy | Don't know |
|--|--|-------------------------|------------------------------|--------------------|------------|
| Active RFID | 10.5% | 2.6% | 18.4% | 39.5% | 28.9% |
| Passive RFID | 5.3% | 10.5% | 7.9% | 42.1% | 34.2% |
| Sensors – temperature, humidity, vibration | 36.8% | 0.0% | 21.1% | 21.1% | 21.1% |

Table 6 — Practitioner technology adoption

Vendor technology adoption

This perspective was supported by the responses by the vendor community. Providers of RFID, sensor technology – or related software – for the clinical trials process appear to be less prolific than in other healthcare industry sectors surveyed. In terms of actual implementations, there is still a long way to go before this technology is ‘mainstream’ – reflected in the following responses:

| What is the time-frame for your typical customers' deployment | Already deployed (pilot or production) | Deploy during 2006-2007 | Deploy during 2008 or beyond | No plans to deploy | Don't know |
|---|--|-------------------------|------------------------------|--------------------|------------|
| Active RFID | 6.3% | 3.1% | 43.8% | 21.9% | 25.0% |
| Passive RFID | 3.1% | 9.4% | 43.8% | 18.8% | 25.0% |
| Sensors – temperature, humidity, vibration | 34.4% | 6.3% | 25.0% | 9.4% | 25.0% |

Table 7— Vendor technology adoption

In Conclusion

Outsourcing, globalization and other factors that impact all areas of supply chain management have created additional challenges in the area of clinical trials and commercialization of pharmaceuticals and treatments. The extended network of participants that are engaged in the evaluation, monitoring and control of these experimental drugs and biological compounds needs to have access to the data related to each of the critical functions – especially those preceding and following their specific area of involvement. Information gathered during the pre-clinical process is critical, and forms the framework for the development of samples of the experimental compounds, packaging these in configurations that will protect them through the clinical trials process. This includes data related to packaging, storage, transportation and other factors that could impact the ‘state’ of the compounds that are being evaluated. This same information is equally important when ramping up for production once the product achieves approval.

The technology already exists to create a ‘single version of the truth’ where all participants have access to the data required to streamline the process from discovery to disposition. However, there are many challenges and learnings that must take place.

The steps to move towards reaping the benefits of RFID in clinical trials:

- Get education first before diving into technology – there is a lot to learn
- Start now, start small, focus on one area with high ROI
- Plan from reality, not market hype
- Start with business drivers and process, not with technology
- Conduct a pilot study under controlled but real world conditions
- Test, learn key lessons – what you don’t “see” *can* hurt you
- Work out the “physics” issues before leaping to production
- Don’t underestimate the critical need for change management



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Addendum 1 - Overview of Technology Components

RADIO FREQUENCY IDENTIFICATION

RFID is a relatively mature technology that promises to provide one of the solutions for automating data collection in Clinical Trials.

| Solution Component | Description |
|----------------------------------|---|
| RFID Tag (or Transponder) | A microchip attached to an antenna that both picks up signals from and sends signals to a reader. The tag contains a unique serial number, and may have other data. |
| Antenna | The antenna is the conductive element that enables the tag to send and receive data. |
| Reader/ Interrogator | The reader (also called an interrogator) communicates with the RFID tag via radio waves and passes the information in digital form to a computer system. |
| Active Tag | RFID tag that contains its own power source. This power source is used to power the microchip and transmit data. |
| Passive Tag | An RFID tag that is powered solely by the RF energy emitted by the reader device. The passive tag uses this energy to power the microchip and transmit data. |

Table 8 — RFID Solution Components

TEMPERATURE MAPPING AND CONTROLS

- **Temperature Monitors**

Electronic temperature monitors provide complete time and temperature data for tracking perishable products.

- **Active Tags**

Active Tag technology is a radio frequency-enabled temperature monitor that is capable of recording the condition, time and location of products in real to near real-time as they move between locations.

- **Strip Chart Recorders**

Affordable and highly accurate temperature recorders which provide a permanent record of temperature fluctuations that may threaten the quality of products and profits.

- **Specialized Labeling**

This includes the adoption of temperature-sensitive labels, as well as color-coded labels to identify Cold Chain product.

This is in addition to the specific labeling requirements for clinical trials – with compliance to Directive 91/356 as amended for Investigational Medicinal Products. The following information should be included on labels, unless absence of its contents can be justified:

- Name, address and telephone number of the sponsor.
- Pharmaceutical dosage form of the drug, route of administration, quantity of dosage units, and (in the case of open trials) the name/identifier and strength/potency.
- The batch and/or code number identifying the contents and packaging.



- A trial reference code allowing identification of the trial, site, investigator and sponsor, if not given elsewhere. The trial subject identification number/treatment number and (where relevant) the visit number.
- The name of the investigator.
- Directions for use.
- "For clinical trial use only" or similar wording.
- The storage requirements.
- Period of use (use-by date, expiry date or re-test date as applicable), in month/year format and in a manner that avoids any ambiguity.
- "Keep out of reach of children" except when the product is for use in trials where the product is not taken home by subjects.



SMART PACKAGING

RFID, scaled down organic light-emitting diodes (OLED) displays, sensors, thin film batteries and photovoltaics are among the printable technologies that can be used in packaging to make pharmaceutical products healthier, more secure, longer-lasting and easier to use. Significant improvements in the ability of printing machines to create RFIDs in high volume and print them on a wide variety of substrates will be key to achieving the price targets for technology components. In the past, the evolution of smart packaging has been hampered by the lack of small, low-cost power sources. The following provide relatively low-cost alternatives

- piezoelectric materials
- organic photo- voltaics
- thin film batteries

Shape memory alloys will control the opening and closing of packages depending on environmental conditions.

Piezoelectric materials will provide power for lighting and audio features on packaging, and smart adhesives can be used in conjunction with smart labels to ensure freshness through color changes.

Benefits of smart packaging

Smart Packaging will facilitate the collection of reliable data, ensuring that patients take medication on the timetable and frequency required, and avoid non-compliance issues that could provide incorrect clinical trial results.

Example:

IMC's eCAP RFID technology, developed so that researchers could track medication usage during clinical trials without active patient input, by using an RFID "smart tag" embedded into a standard medication bottle cap, which records the time at which the bottle is opened by the patient to remove their prescribed dose, thus logging the patient's medication use.



IMC has also developed Med-ic ECM (Electronic Compliance Monitoring) packaging – a disposable, low-cost intelligent pharmaceutical packaging (IPP) monitor for blister-packaged medication, which uses a sensor grid technology and a proprietary process of printed conductive inks to record the time a pill or capsule is expelled from the package.

Suppliers of 'smart packaging' include: Information Mediary (IMC), Meadwestvaco, Cypak, En-vision America, MedivoxRx, Supplyscape, Zars, SmartSensor Telemed, Lifeline Technology, CliniSense.

Addendum 2 - Sample Drug Company Pipeline

THE GENETECH PIPELINE (JUNE 2006)

As a biotechnology leader, Genetech has a long-standing tradition of reinvesting a significant percentage of revenues back into research and development – a practice that has proven successful in transforming promising candidates into important new products.

Awaiting FDA Action

- **Avastin®** - second-line colorectal cancer
- **Lucentis™** - wet age-related macular degeneration
- **Rituxan® Immunology** - rheumatoid arthritis (anti-TNF inadequate responders)

FDA Filing Preparation

- **Avastin®** - First-line metastatic breast cancer
First-line non-squamous non-small cell lung cancer
- **Herceptin®** - Adjuvant breast cancer
First-line metastatic breast cancer in combination with Taxotere
- **Rituxan® Hematology/Oncology** - indolent frontline/maintenance NHL

Phase III Clinical Trials

- **Avastin®** - Adjuvant breast cancer
Adjuvant colorectal cancer
Adjuvant non-small cell lung cancer
First-line metastatic breast cancer
First-line ovarian cancer
First-line pancreatic cancer
First-line renal cell carcinoma
Hormone refractory prostate cancer
Second-line metastatic breast cancer



- **Rituxan® Hematology/Oncology** - relapsed chronic lymphocytic leukemia
- **Rituxan® Immunology** - ANCA-associated vasculitis
 - Lupus nephritis
 - Rheumatoid arthritis (DMARD inadequate responders)
 - Primary progressive multiple sclerosis
 - Systemic lupus erythematosus
- **Tarceva®** - Adjuvant non-small cell lung cancer
- **Tarceva® +/- Avastin®** - Second-line non-small cell lung cancer
- **Xolair®** - Pediatric asthma

Phase II Clinical Trials

- **2nd Generation Anti-CD20** - Rheumatoid arthritis
- **Avastin®** - Glioblastoma multiforme
- **Avastin® +/- Tarceva®** - Second-line non-small cell lung cancer
- **Omnitarg™** - Ovarian cancer
- **Rituxan® Immunology** - Relapsing remitting multiple sclerosis
- **Topical VEGF** - Diabetic foot ulcers
- **Xolair®** - Peanut allergy

Phase I Clinical Trials

- **Apo2L/TRAIL** - Cancer therapy
- **BR3-Fc** - Rheumatoid arthritis
- **Topical Hedgehog Antagonist** - Basal cell carcinoma
- **Trastuzumab-DM1** - HER2+ metastatic breast cancer

Pre-IND

- **Anti-BR3** - Chronic lymphocytic leukemia
- **New Molecular Entity (2)** - Oncology (TBA)
- **New Molecular Entity** - Immunology (TBA)





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