

This article provides a straightforward step by step approach for gradually implementing PAT in existing manufacturing processes.

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Implementing PAT Step by Step as a Process Optimization Tool

by Connie Langberg Heinze and Jan Ruud Hansen

Introduction

Process Analytical Technology (PAT) is a very important framework focusing on improved process understanding and process knowledge. It is the key to help the pharmaceutical and biotech industry move toward continuous process improvements and small scale manufacturing in the future. Focus on process understanding can reduce the validation burden by providing more efficient options for justifying and qualifying systems intended to monitor and control biological, physical, and/or chemical attributes of materials and processes.¹ In a PAT framework, process validation does not exist in the way it does now. The manufacturing processes will be monitored and controlled with qualified equipment. In 5-10 years from now, 95% of the quality control will be on-line measurements, and that will lead the industry into continuous process improvements.²

According to the FDA, this is described as: "The desired future state of the pharmaceuti-

cal manufacturing," - *Figure 1.*³

The FDA is actively involved in guiding the industry to understand and adopt this new paradigm in order to reach the desired state. The FDA is involved in several organizations like ASTM Committee E55 on Pharmaceutical Application of Process Analytical Technology and International Forum of Process Analytical Chemistry (IFPAC). FDA also works closely with ISPE in the FDA/ISPE PAT Forums.

The following quote from an article in the ASTM standardization news in May 2004 by Christopher Watts, Ali Afnan, and Ajaz Hussain from the FDA emphasizes that product specifications based on a scientific and mechanistic process understanding can be established by taking advantages of innovation and new technologies. "PAT represents the FDA's vision for future pharmaceutical product development and manufacture. As pharmaceutical development and manufacturing evolves from an art form to one based on science and engineering, the FDA will use the knowledge developed in

PAT to establish product specifications and evaluate manufacturing processes. This is an opportunity to create improvements in the productivity of both manufacturing and regulatory processes.^{4"}

Today, the specifications are generally described in terms of discrete or attribute data (pass/fail or as an interval). The quality assurance is based on whether the analysis result of a sample is within the specification limits.

In a PAT framework, the specifications are defined by a risk-based approach based on patients needs and not accord-

Figure 1. Desired state.

Desired State

The desired future state of the pharmaceutical manufacturing may be characterized as:

- Product quality and performance achieved and assured by design of effective and efficient manufacturing processes
- Product specifications based on mechanistic understanding of how formulation and process factors impact product performance
- Continuous "real time" assurance of quality
- Regulatory policies and procedures tailored to recognize the level of scientific knowledge supporting product applications, process validation, and process capability
- Risk based regulatory scrutiny that relates to the level of scientific understanding of how formulation and manufacturing process factors affect product quality and performance and the capability of process control strategies to prevent or mitigate risk of producing a poor quality product.³

Process Analytical Technology is a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality.

Definition of PAT from the FDA/CDER Web site, last updated 7 February 2005 - <http://www.fda.gov/cder/OPS/PAT.htm>

ing to the capability of the process. With the new measurement technologies, it is now possible to measure directly on the product in real time and receive a signature of the product and compare this signature with a reference just like a fingerprint recognition test.

Feedback loops to change the specifications and the critical attributes along with the increased process knowledge are required and are an important part of continuous improvements. Don't waste time on things that are irrelevant to the quality of the product. Always ask, what is critical to the patient safety and the product quality.

It is important to realize that a successful PAT implementation is a multifunctional exercise in the organization covering manufacturing, research and development, quality control, quality assurance, and regulatory affairs.

These disciplines are all involved in the implementation. The PAT framework will affect the way people work together in the organization. Therefore, reorganizations will most likely be a part of the PAT implementation.

Implementation Step by Step

We anticipate that monitoring and controlling the process quality in the pharmaceutical industry will be very different in the future.

But how will we get there? The ideal way to start is probably to implement PAT to a new product as an integrated part of the process design in the development phase. The advantage of that approach could be that there are no regulatory constraints. By that time, one will have the *opportunities to improve the mechanistic basis for establishing regulatory specifications*,⁵ but there are also disadvantages namely the lack of data, experience, understanding, and knowledge of the product and process and the risk of increasing time-to-market if the PAT implementation fails.

Another way to approach this new way of working is to start in an existing manufacturing process. Then, little by little, start the implementation and gain the necessary knowledge and understanding of the PAT framework. In this case, there are historical data and knowledge to use as a basis for building up the PAT competences. One could argue that it is too risky to jeopardize an existing product, but the FDA has opened a door as they stated in the PAT guidance⁵ that when implementing PAT in an existing process, the PAT application can be used as an add on solution. The collected data will be regarded as research data until the manufacturer is

comfortable with replacing the existing batch release test with the PAT application and making that the batch releasing measurement.

Currently, the industry is at the level of descriptive and correlative process knowledge. What is going on in the process and what process output correlates to which input? Mechanistic process understanding is answering what causes the correlations to occur and how did it happen? The result of process understanding is that all critical sources of variability are identified and explained. Variability is managed by controlling the process, and product quality attributes can be accurately and reliably predicted. In order to obtain the process understanding in a mechanistic way as described in the PAT guidance,⁵ the entire manufacturing process and all the risks in the process must be taken into consideration.

Before starting the PAT implementation, it is very important to define a strategy including a mission statement and some objectives for the PAT implementation. The strategy should be presented to the top management in order to get their commitment and approval for spending financial and human resources on PAT. The strategy will include consideration of the following:

- how to approach PAT in the company
- who will be involved
- which process and or product to begin with
- what do we expect to benefit from the implementation
- what are the needed financial and human resources

Once the mission statement, objectives, and budget are approved by the management, it is time to begin the implementation step by step. One way to begin the PAT implementation is to identify one or two of the biggest problem areas and start the PAT implementation there. In this article, a PAT step by step implementation plan is presented. This implementation plan is just one way to do it, but certainly not the only way - *Figure 2*.

Form the PAT Team

Gather a group of experts with representatives from development, manufacturing, quality control, quality assurance, and as an option, regulatory affairs, and let them form a PAT implementation team. A data analyst/statistician should be represented in the team as well. It is recommendable to have a facilitator to see the implementation from an overall perspective. When the PAT framework is fully implemented, it will imply new ways of working in the company, and it can be difficult for people involved to be objective all the way through the implementation, once they realize that their job role will change and new skills will be required after the PAT implementation. It is important to include motivation and change management in the implementation plan. The facilitator also may be the contact person to FDA or other authorities.

Review Processes

The PAT implementation team should review the entire manufacturing process using a risk-based approach in order

to identify the process step or steps with the highest potential to reduce risk and improve quality.

The process review should include:

- flowcharts of key manufacturing processes showing current control points
- data analysis of historical data maintained in regulatory records with focus on sources of variability
- identification of critical quality attributes and process control points by risk assessment
- an overview of Out Of Specifications (OOS)/nonconformities/Corrective And Preventive Actions (CAPA) and possible causes
- evaluation of the specifications with a risk-based approach
- identification of scrap
- identification of low yields and high variability in the process

Analyze historical data by going through the batch records and the LIMS system; use a multivariate data analysis tool to find correlations and possible problem areas. If the analysis of the historical data reveals correlations, process understanding can be improved. Just to take a very simple example. For instance, by correlating the in-process pH data of the solvents with the result of yield in a chromatography step, one might find, that if the pH is in the lower end of the interval (still within the specification limits), the yields are higher.

The use of Statistical Process Control (SPC) techniques also is helpful in this analyzing phase. Remember, that it is not only the Out Of Specification (OOS) results that need to be looked at, but also look for processes which are not in statistical control (e.g., trends). For instance, if you have seven batches and the results of the purity are lower for every batch, but all results are within the lower specification limit, it is still important to check what was special about these batches. Did we use another batch of raw material?

The next step is to do a risk assessment on the process step using for example Hazard Analysis Critical Control Points (HACCP) or Failure Mode Effect Analysis (FMEA). These are both recommended tools to secure focus on the product and process risks. The output of the risk assessment is identification of the critical control points of the process step.

Prioritize and Define Pilot Project

The outcome of the process review is a project catalogue outlining the opportunities for the PAT implementation. An overall cost/benefit analysis should be included in the process review. A detailed cost/benefit analysis can be difficult to perform at this stage, when the needs for instrument and tools investment are unknown, but a rough estimate is recommended.

Do not aim at making a finished project catalogue before continuing with the next steps for already identified, acknowledged, and prioritized opportunities for improvement. Remember that ensuring and improving product quality and process efficiency is an ongoing continuous process.

It is important to prioritize the different projects in order to obtain the most value for the time, resources, and investment spent on the project. The prioritizing can be performed by evaluating the complexity against the expected benefit. This evaluation must be performed with a risk-based approach. A number of pilot cases are selected depending on the

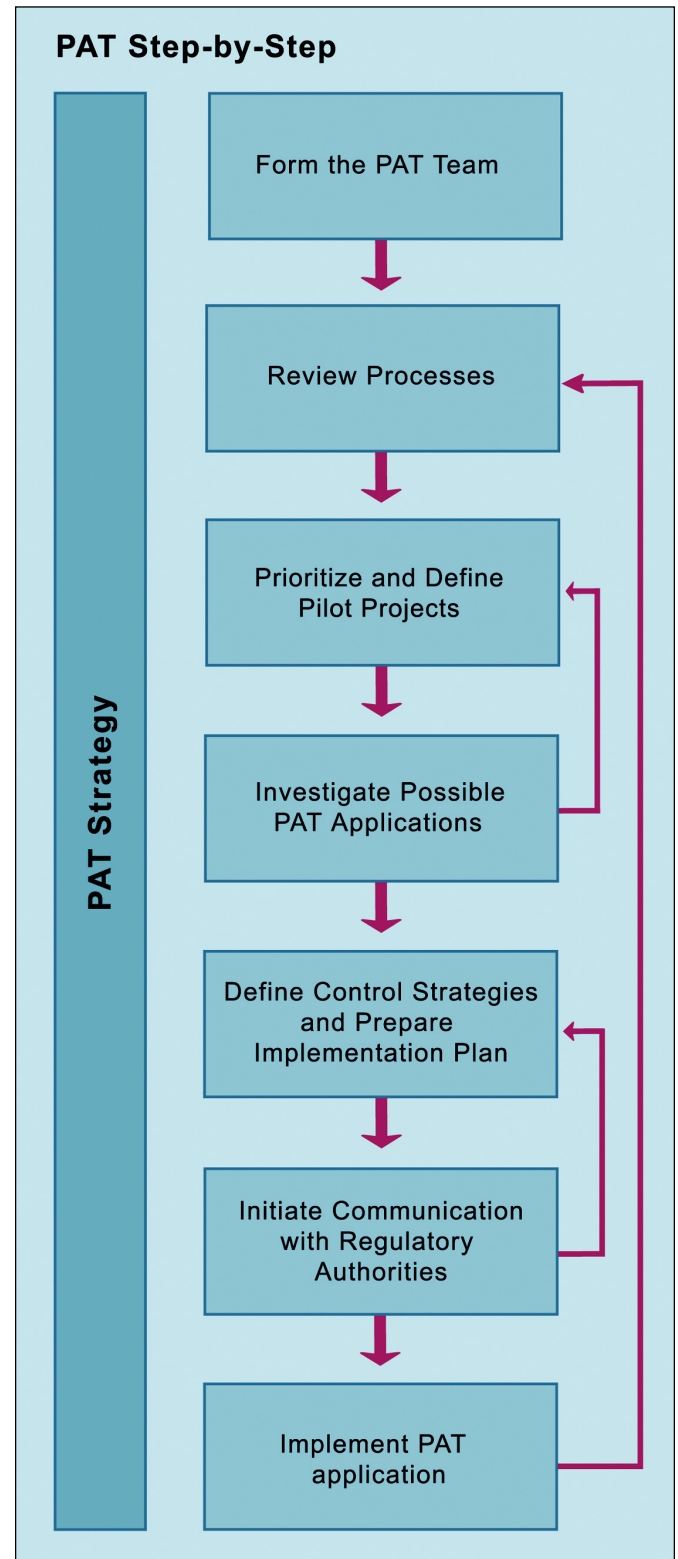


Figure 2. PAT step by step.

financial and human resources and the competences in the company.

Investigate Possible PAT Applications

From the process review step, you should have a fairly good idea of what you need to measure and control. After the process review, it is possible to prepare the requirement specification for the PAT application and start the investigation of possible PAT applications.

Do not limit your investigation to process analyzers only. Tools for data analysis, process control, continuous improvement, and knowledge management are equally - if not more important in order to reduce variability in the manufacturing process.

This may not; however, be the right time for making company wide strategic decisions regarding IT systems and infrastructure for the support of PAT applications.

Take advantage of the work that has already been done and published. Use the experience in house and from other companies as a starting point.

Find possible suggestions for analyzers or other measurement techniques facilitating real time measurements by searching in literature and conference presentations to be sure that the instruments and techniques have proven records as PAT tools. Contact suppliers and discuss the specific applications with them and arrange a demo of the most promising solutions. Process parameters like concentration, physical and chemical conditions in the measuring environment will be important factors in determining the most suitable solution. The specificity and sensitivity of the instruments are obviously important factors when looking for possible solutions. If we, for instance, are looking for an on-line measurement of solvent concentration to control the gradient in a chromatography step, the use of conductivity might be too sensitive to temperature and not specific enough to control the solvent concentration. NIR could be a better suggestion for that purpose.

When a list of possible solutions is prepared, factors like price, user friendliness, and installations complexity can be taken into consideration. Prioritize the list by giving the different factors an importance index and evaluate each possible solution against the different factors.

Define Control Strategies and Prepare an Implementation Plan

Develop a model for measuring the specific parameter in cooperation with the supplier of the equipment or a consultant. The use of a multivariate data analysis tool can help interpret the data to a number or a process signature. It is important to develop a standard or reference to calibrate and measure against. The model is often developed in lab or off-line, in order not to disturb the manufacturing.

The model development also will include a control strategy. How will the data be used? Define the feedback loop to the input process parameter in order to minimize the output process variability.

Once the model is developed and you know that the

application will work, a detailed implementation plan is prepared. The plan should answer questions like:

- When will we start?
- How will the installation affect the quality of the product?
- What data will be documented in the batch report in the future?
- What data will be collected?
- How will this installation be documented - just as part of the regular change control procedure or do we need to send in an amendment to the authorities?

If the measurement replaces an analysis or another measurement, a comparability study is needed. Under all circumstances, it is important that a risk analysis is conducted and documented to evaluate the impact of the product quality before installation.

Consider the implementation of an on-line Statistical Process Control (SPC) system (data analysis) as part of the control strategy. Once gathered, this data can easily be analyzed using multivariate techniques such as Principle Component Analysis (PCA) and Partial Least Squares (PLS). Simple plots allow the site engineer not only to monitor the manufacturing of a batch, but also understand the sources of variations between batches of product.

With a statistical stable process, a calculation of the Process Capability (Cpk) will be informative. Process capability compares the output of an in-control process to the specification limits by using capability indices using both the process variability and the process specifications to determine the capability. The process capability measures how close the result is to the target and how consistent the result is around the average performance. The larger the Cpk index is, the less likely it is that the results will be outside the specifications.

Initiate Communication with Regulatory Authorities

Once the implementation strategy is prepared and before any instruments are implemented in the process, it is very important to contact the FDA PAT team or other corresponding authorities in order to discuss the implementation plan. Ask questions and tell what has been done and what will be done. That will give you the confidence that they will approve the changes next time they come by for an inspection and minimize the risk of insufficient evaluations and documentations. Depending on the outcome of the discussion with the FDA or other authorities, the implementation plan might be revised.

PAT Implementation

A qualification protocol, test, and report have to be prepared. Again, it is very important to do this from a risk-based approach to verify that the instrument or tool and the application is designed, implemented, and performs as specified in the requirement specification.⁶ Always ask what is critical to the product quality.

In a PAT environment, three batches of process validation

makes no sense. Validation is demonstrated through continuous quality assurance by measuring the critical product quality attributes in real time with qualified equipment. Instead of taking samples and bringing them to the laboratories for analysis, the entire product stream can be tested with qualified equipment, and, if necessary, the process input can be adjusted in order to get a more consistent output. This is a more reliable way to determine and ensure product quality than to perform a three batch process validation.

It is a good idea to discuss the protocols with the FDA or other authorities to be confident that the documentation is adequate for the approval of the application.

For a period of time until the PAT application is fully implemented, the collected data will be seen as research data. During the research period, it is important to continue the old way of sampling and analyzing because the data from the PAT application will not be accepted as batch release data before the submission of the PAT application is approved by FDA or other authorities. Use this period to collect relevant data and expand the knowledge of the process. Determine or redefine the control strategy to ensure that variations in the process input are controlled to make consistency in the process output.

When the control strategy is decided upon and the PAT application is approved by the FDA or other authorities, the PAT application can be regarded as implemented for quality control and the data can be used for batch release. The research data period can be short or long, depending on the complexity of the application, the success rate, and the risk the company is willing to take by implementing the application.

When you have come this far with the implementation you can go back and look at the next PAT application.

Like with everything else new, one might run into trouble with the new equipment or tools. It is important to perform a risk assessment of the stability and reliability of the PAT application. Do you need a back up instrument, or is it sufficient to have a service agreement with either a consultant and/or the equipment supplier to make sure that the new PAT application is not stopping your production. This evaluation depends on the complexity of the instruments, the track record of the application, and the risk you are willing to take.

Conclusion

It is important to realize that implementing the PAT framework in a company should be an iterative process which will take time, probably several years. Our recommendation is to use the experience and knowledge gained in the implementation of the first PAT application, to go back to the process review, and start with a new process challenge and PAT application. Then, little by little, the process understanding is improved and the new mindset will evolve. The manufacturing, the QC, and R&D staff will be working closely together developing measurement and control strategies for the existing manufacturing processes. Knowledge and experience gained during PAT implementations in an existing process can be transferred to the development phase of new

products and processes.

Continuous improvement will be part of the manufacturing as a result of implementing PAT step by step. Variability is minimized or eliminated and processes will be developed based on a scientific and mechanistic process understanding.

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This article presents a novel check-weighing technique which measures the mass contents of each individual container using NMR.

In-Line Non-Contact Check-Weighing (NCCW) with Nuclear Magnetic Resonance (NMR) Presents New Opportunities and Challenges in Process Control

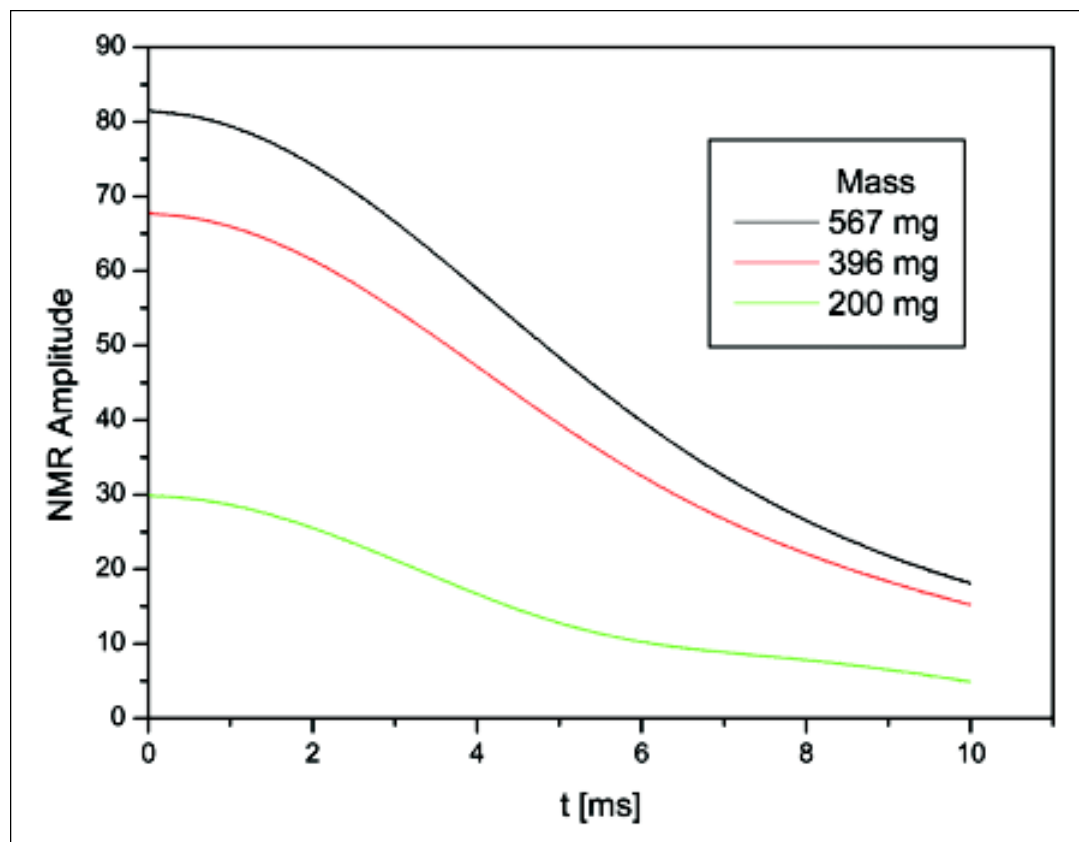
by Jos Corver, Gisela Guthausen, and Andreas Kamlowski

Introduction

The principle of Process Analytical Technology (PAT) is that *quality cannot be tested into products; it should be built-in or should be by design*. The goal of PAT is to specify, monitor, and control processes to consistently ensure a predefined qual-

ity. The FDA is actively supporting this initiative, which represents a change in focus away from data-related validation toward a process approach. It is therefore essential to assure well-controlled and predictable processes, and to this end, the accurate measurement of critical parameters plays a prominent role.

Figure 1. NMR signals of a liquid with the amount of fluid as a parameter. It is clearly visible that the NMR amplitude correlates with the sample's weight. In this example, data from the most simple NMR experiment (an FID) was performed. The signal decay is due to the magnet's inhomogeneity and not a feature of the sample.



“It is essential for in-line process control that critical parameters are monitored continuously without disturbing the process or compromising the product.”

A number of filling principles can be used for high-speed aseptic filling of liquids (rotary pumps, peristaltic pumps, time-pressure) or powders (auger or vacuum-blow). Such systems are equipped with In Process Control (IPC) involving weighing systems. Balances are widely used for this purpose. Because balances need some settling time, it is usually not possible to implement 100% weight checking in filling lines. The control process is therefore reliant on statistical check-weighing. Furthermore, the sensitivity of the balances to vibration, static electricity, air-flow, and pressure fluctuations limits the achievable accuracy. In order to establish a net weight, the same vial needs to be weighed empty and filled and the results of both weights subtracted, which requires sampled vials to be taken from the mainstream twice and potentially constitutes a different process. Balances are precision instruments that can be potentially disturbed easily during manual intervention, such as change-over and cleaning.

It is essential for in-line process control that critical parameters are monitored continuously without disturbing the process or compromising the product. Accordingly, technologies for non-invasive measurement of critical parameters that are traditionally associated with the laboratory environment are being engineered for duty in the production area. Nuclear Magnetic Resonance (NMR) is one of these non-invasive technologies. NMR is associated with applications in drug discovery and structural biology as well as the clinical environment, such as Magnetic Resonance Imaging (MRI) and analysis of blood. Numerous NMR-based quality control applications exist in the chemical, petro-chemical, food, and agricultural industries, in which bench-top NMR systems are utilized.

The system described herein has been developed to measure the weight of product in glass vials while in motion in a production filling system. 100% sampling is performed to assure that all vials have been filled to within the required weight limits and all product experiences an identical processing environment. The data collected also can be used for process control purposes. In contrast to weight measurements with precision balances, NMR can determine the net weight of the drug in the vial with a single measurement, without taking the vial ‘out of line’ since the container materials can be filtered out. NMR derives the weight at full line speed without making physical contact with the vial and for this reason the method has been termed Non-Contact Check-Weighing (NCCW).

The Value of 100% Measurement

Although the benefit of 100% inspection is subjectively appreciated, it can be quantified as well. In this paragraph, the

quality assurance perspective, the economic perspective, and the process reliability are taken to illustrate this.

- **QA Perspective:** It is common practice that a manufacturing (filling) process is ‘well-behaved’ if its associated C_{pk} is at least 1.33, indicating that the target fill is above the Lower Specification Level (LSL) four times the Standard Deviation of the filling process (sigma, SD). The Upper Specification Level (USL) will not be considered in this context:

$$C_{pk} = (\text{mean} - \text{LSL}) / (3 * \text{SD}) \geq 1.33$$

with LSL and USL being Lower Specification Level and Upper Specification Level respectively and sigma the standard deviation of the filling process. In a good number of occasions only the lower specification level (or label claim) is the actual point of interest. In that situation, this required C_{pk} of 1.33 is identical to stating that the target fill setting is at least 4 * sigma above the label claim. However, this does not guarantee that no container will be under-filled. Under the assumption that the fill-distribution is a statistical process with a normal probability distribution, 6 out of 100,000 fills will fail the label claim and not be detected. Another issue is the procedure to be followed when a reject is found with a statistical sampling process. Whether or not the number of products between this rejected and the previous last accepted product is to be rejected, is a matter that deserves some attention.

- **Economic Perspective:** Given the starting point which is described above, i.e. making the filling set-point 4 * sigma above the label claim, it is clear that on the average too much product is supplied to the batch of containers. With the use of 100% measurement, it is possible to reduce the filling set point and obtain a higher number of filled containers. On the downside, there is an obvious number of fills below the label claim that will be detected and rejected. It is always possible to find an optimal filling set point yielding a higher number of filled containers, compared to the initial situation.
- **Process Reliability:** When the 100% measurement system is part of a control loop to adjust the filling process, the stability of the process is enhanced. There is a lot of flexibility for implementing the feedback mechanism. Since usually drift destabilizes the filling process, it is possible to average over a number of fills and acquire a high resolution that can be applied to the correction. Compared

'Traditional' filling line	Filling line with NMR system	Remarks
Washing station	Washing station	Remove particles and soluble substances
Depyrogenation tunnel	Depyrogenation tunnel	> log6 reduction of endotoxins
Infeed system	Infeed system	Align vials in a single row
'Tare' weighing robot		Weigh empty vial (2% of population)
Filling module	Filling module	Filling system can be time/pressure, rotary pump, peristaltic pump, auger, vacuum-blow etc.
'Gross' weighing robot		Weigh filled vial (2% of population)
Stoppering system	Stoppering system	
Reject/sampling system	NCCW, non-contact check-weighing NMR system with integrated reject/sampling system	Weigh contents of vials (100% of population) (stopper and vial are not 'visible')

Table A. Modules in a filling line.

to feedback systems that use 1% sampling, this 100% system will be 10 times better (statistically).

NCCW Principle

The principle of operation of analytical balances is generally based on an electromagnetic compensation circuit, where the compression of a spring by a mass is compensated by an electromagnetic force. The electric current required to generate this electromagnetic force is a measure for the weight and this current is calibrated against reference masses. The principle of NCCW with NMR is equally easy to grasp, but since NMR nomenclature is not common, some background to the technology is explained in an appendix to this article.

The main features of NMR in the context of NCCW can be summarized as follows:

- NMR is non-destructive (compare also to MRI)
- NMR is quantitative
- NMR is not influenced by surface-texture or color (unlike NIR for instance)
- NMR is a fast detection method (information can be gathered in milliseconds, unlike balances)

- NMR can measure minute differences in sample compositions
- NMR can directly measure a sample's mass once calibration has been performed

As the name indicates, a magnetic resonance signal is obtained from the sample in the NMR probe; or more precisely, from the magnetic moments associated with nuclear spins. In most cases of bench-top NMR, the nuclear spin of the hydrogen nucleus is targeted because of its ubiquitous availability and the high natural abundance of the isotope ^1H (>99.9%).

If a sample with a certain number, N , of ^1H nuclear spins is placed in a static magnetic field, of strength B_0 , a net magnetization M_0 will result. The relationship (known as the Curie-law) is:

$$M_0 = \text{Constant} \cdot (N/T) \cdot B_0,$$

(T is the absolute sample temperature in Kelvin). Therefore, the NMR method applied in NCCW is simply a measure of the magnetization M_0 . The more nuclear spins in the sample, the higher the magnetization M_0 . Calibration of the magnetization M_0 with samples of known mass (and a defined composition) will lead to an NMR-based 'balance,' viz NCCW.

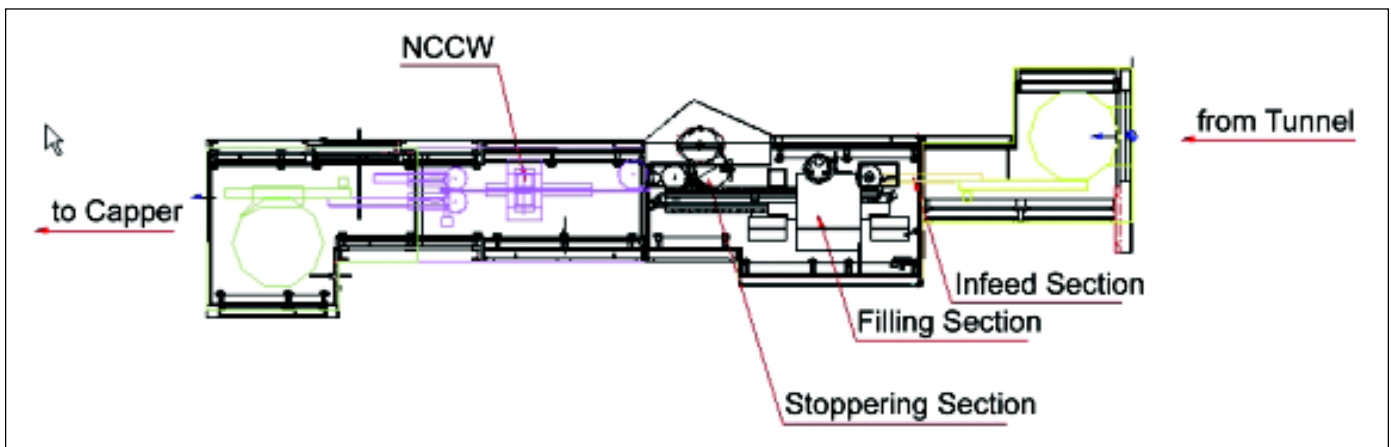


Figure 2. Typical layout of a filling line with focus on the NCCW.

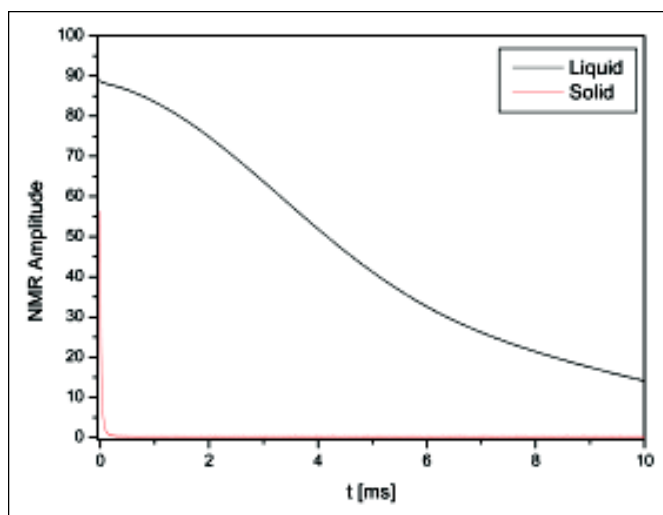


Figure 3. Decay of the observable magnetization (^1H -FID) of a liquid sample compared to a solid.

In order to demonstrate this relation between the NMR signal and the number of hydrogen nuclei in a substance, resulting in the sample's weight, three liquid samples of known mass are measured by bench-top NMR - *Figure 1*. The NMR amplitude is related to the mass. Calibrating the NMR amplitude against the sample's mass allows mass determination of unknown samples.

Filling Line: System Description including NCCW

In Table A, a comparison is made between a traditional filling line and a line that contains an NCCW system for checkweighing.

The main advantage of a filling line with NCCW is that 100% checking can be achieved, providing the most comprehensive in-line quality and production control data. Furthermore, timely feedback of data for process control is available.

To achieve these advantages, a number of technical challenges have had to be overcome:

- magnet temperature stabilization
- selection of 'NMR-dark' materials which are compatible with pharmaceutical requirements
- undesirable signals from (e.g.) the stopper, vials adjacent the vial to be measured (called near-neighbor effect)
- motion-related effects

Magnets and Temperature

The magnets that are used traditionally in bench-top instruments are permanent magnets. However, the magnetic field provided is temperature dependent. Since NMR experiments need to fulfill the resonance condition (see Appendix), tight control of temperature is required. Although this is routine in bench-top NMR (where temperature can be controlled to one-thousandth of a degree Kelvin) its applica-

tion to NCCW is more complex in that a combination of insulation and temperature stabilization and regulation needs to be provided. The magnet also has to be freely accessible from at least the direction of travel of the vials. If the NCCW is to be placed in the isolator, also the vertical direction has to be clear for the laminar air-flow system and for cleaning purposes.

NMR-Dark Materials

In developing a conveyor to operate in an NMR environment, the choice of materials is limited. Vial conveyors are mostly made of stainless steel with polymer belts. Specific high-quality steel has to be selected which will not interfere with the magnetic field. Moving metals need to be avoided since they induce eddy-currents which disrupt field homogeneity. In essence, this means that the conveyor belt and pulleys have to be non-metallic. Ideally, the belt passing through the NCCW system should be made from a hydrogen-free material which will fulfill mechanical requirements.

Undesired Signals

Several circumstances complicate the picture of NMR outlined above since almost all materials contain protons (hydrogen nuclei) to a greater or lesser extent. The total signal amplitude is the sum of the contribution of each spin within a certain sample volume, and therefore, the desirable and undesirable signals interact. Techniques for signal separation have had to be developed, and specific to NCCW on closed vials, four prime interactions need to be considered:

- the sample to be weighed produces a signal
- the rubber of the stopper produces an NMR signal, which is undesirable

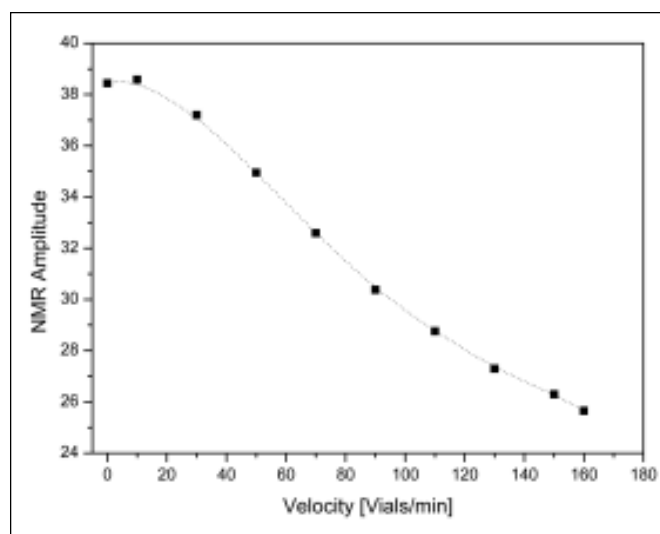


Figure 4. Velocity dependence of the NMR response of solid samples. The magnetization is maximum at very low speeds and it decreases rapidly with increasing speed. This is due to partial magnetization built up in a magnetic field. The polarization length amounts to about 3 cm, T_1 is in the order of 850 ms.

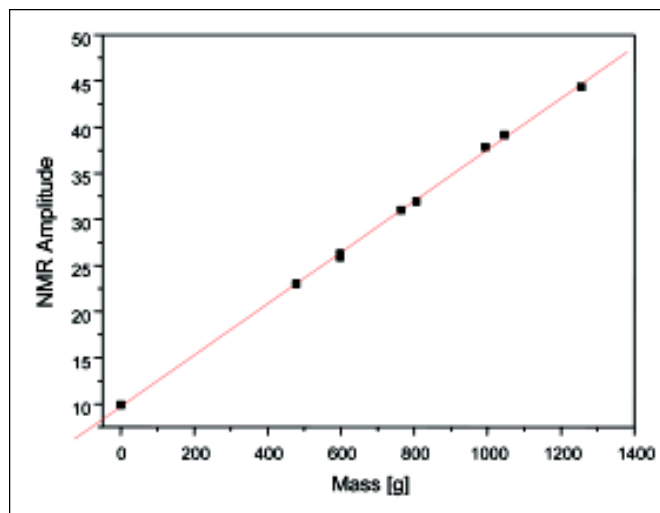


Figure 5. Typical calibration line for solids.

- preceding and following vials (near neighbors) can contribute a signal when in close proximity to the sample vial
- background signals from the belt and other parts in the RF field need to be avoided. If they cannot be avoided, they at least have to be minimized and kept constant

Two approaches can be used:

1. spatial separation
2. temporal separation

In the case of spatial separation, the magnetic RF-field produced by the NMR probe is restricted to the region of the sample only, effectively suppressing undesired signals from the stopper and near-neighbors. The challenge here is in not compromising the performance of the NMR probe to detect the desired signal from the sample. In the third dimension, which is across the vial, a flat RF profile is required so that all protons are equally weighted. These effects call for sophisticated design of the NMR probe.

Closer inspection reveals that the RF profile along the direction of travel of the vials is most challenging since a sharp profile is required to effectively suppress NMR signals from neighboring vials. The magnetization of following vials is dependent on their 'NMR history' since they have been already subjected to NMR measurements during their approach. Experiments demonstrated that in order to suppress the contributions of the neighbors, the damping factor has to be at least 25 dB at the positions of precursor and follower. There are instances where this approach is not sufficient, in which case near-neighbor contributions can be taken into account by the calibration because the effects are deterministic.

In the case of temporal separation, Figure 3 shows the underlying principle: the NMR response of a solid sample decays faster than that of a liquid state sample (an FID experiment was conducted, see Appendix). Suppose the rub-

ber stopper has characteristics similar to the solid sample, and the sample of interest is a liquid. Clearly, the NMR signal, at times greater than about 0.2 ms, will effectively be free of any contribution from the unwanted stopper. This temporal solution cannot be applied for powder samples and other solid materials. If a background or undesired signal is constant in the framework of the NCCW experiment, it can be taken into account in the calibration process.

Motion-Related Effects

In conventional NMR experiments, the samples under investigation can be considered to be fully magnetized, i.e. the magnetization is in thermal equilibrium (see Appendix). However, in a filling line, the samples enter the NCCW at speed, and it is therefore unlikely that the same magnetization is obtained as in a stationary (conventional) NMR experiment. The velocity of the sample (more precisely the time the sample spends in a given magnetic field) and the time required for build-up of thermal magnetization (the spin-lattice relaxation time T_1 , which is a sample property) determine the magnetization of the sample in NCCW. The NMR signal amplitude is plotted in relation to the velocity of transport expressed as Vials Per Minute (VPM) - Figure 4.

The magnetization decreases with increasing vial speed. In this situation, the signal/noise ratio is negatively impacted by higher vial speeds. One possibility to overcome this is to simply extend the region in which the samples can build-up magnetization. Due to movement of each sample in the spatially limited magnetic field of a 'prepolarizer' arranged along the belt, the achieved magnetization is increased. Ideally, the time the vials are required to stay in the field of the prepolarizer amounts to about three-to-five times T_1 . Space constraints often do not allow a 100% magnetization. The aim is therefore to ensure that each vial has the same 'magnetic history.' To this end, each vial has to be processed at the same constant speed.

This also sets constraints for the detection system that triggers the measurement process of the vials. It needs to be done in a very precise manner in order to minimize the effect of speed variation of the transport system. In an NCCW, a laser sensor is used that detects the presence of the wall of a vial with high accuracy. The NMR experiment is fast (of the order of milliseconds), which at a speed of 600 vials per minute equates to movement of a few millimeters.

NCCW: Examples on Moving Liquid and Solid Samples

Free Induction Decay (FID) is used to determine the contents of vials containing liquids (see Appendix). In Figure 1, the relationship between the amount of liquid and the FID curve is demonstrated when measured in a conventional bench-top NMR system. A similar relationship can be observed in the case of moving liquids. At any point in time, the amplitude of the FID is linearly proportional to the amount of fluid. The resulting accuracy is 0.2% Relative Standard Deviation (RSD) with 1 ml fill. It should be pointed out that by using this

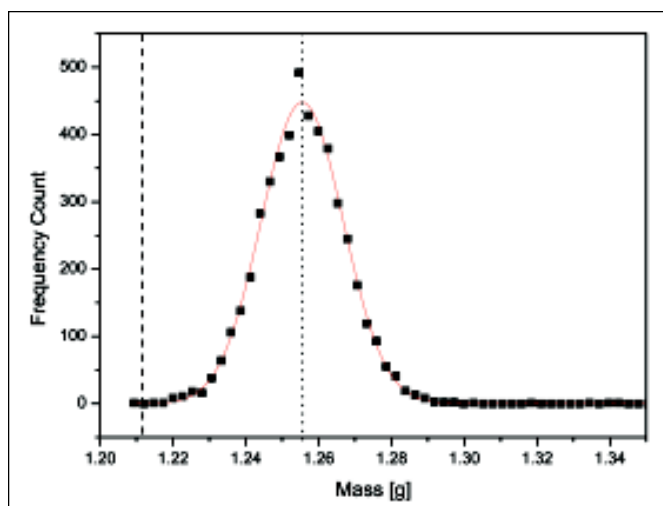


Figure 6. Statistical distribution of about 52000 measured masses. The width of the fitted Gaussian distribution function amounts to 0.022 g, which is identical to $2 \times \text{SD}$. The vertical dotted line describes the mean value of 1.2555 g. Assuming an LSL of $4 \times \text{SD}$ lower than the mean of the distribution function leads to the vertical dashed line (LSL) at 1.214 g. The sample used in this measurement was a powder sample with a nominal mass of 1.2554 g. The measurement was performed without sample movement.

procedure, the mass of the sample in each vial at speeds up to 600 vials per minute can be measured ‘on the fly’ without averaging (using multiple measurements to improve accuracy) or waiting for a balance to stabilize.

In case of ^1H NMR on solid materials, the signal usually decays much faster, as illustrated in Figure 3, from which it could be concluded that the signal/noise ratio is not sufficient to facilitate ‘weighing’ of samples with sufficient precision. Therefore, a different approach has to be taken. In solid state NMR, refocusing techniques are well understood and enable a certain degree of refocusing of magnetization, which would otherwise decay very fast as in Figure 3. This technique can be used to improve signal/noise ratio (see Appendix).

The resulting measured accuracy is 1% RSD for 1 g of powder material. In Figure 5, a typical calibration curve obtained using solid materials is presented. The measurements were performed under static conditions using the refocusing technique. In addition to the low signal/noise, the challenge is to avoid any undesired signal from the rubber stopper while weighing each proton in the sample equally. Due to the nature of the filling process for solid powders, variations in height profile across the vial are to be expected and the RF profile of the NMR probe has to take this into account. Clearly, there is a trade-off between suppression of the signal from the rubber stopper and a non-linear response of the sample at different filling heights.

Illustration of an Implemented System

The filling system in which the NCCW is integrated to has a line capacity of 150 vials per minute. The vials size is 24 mm in diameter with filling heights well below 10 mm. The pitch

amounts to 40 mm leading to a speed of maximum 120 mm/s. The powder sample exhibits particular NMR properties (relaxation times in the order of $T_1 = 900$ ms and $T_{2e} < 120$ μs) rendering application of the refocusing technique necessary (cf. Appendix).

The result of repeated measurements which were performed for validation purposes is shown in Figure 6. The observed distribution function of about 52000 mass measurements is modeled by a Gaussian distribution function which allows a quantitative description of the static reproducibility of this solid NCCW. The Standard Deviation (SD) is 0.1128 g, leading to an RSD of 0.9%. For this example, assuming a difference of $4 \times \text{SD}$ between mean value and LSL (see above), the label claim and the target fill would be 1.214 g and 1.255 g, respectively.

Other Potential Applications

Up to this point, only the application of NMR to measurement of the contents of vials has been considered. Many other applications are feasible which exist already in the laboratory environment, some of which are listed below:

- Application to other packaging forms. It is clear that ampoules do not pose specific difficulties in NMR terms and potentially carpoules and syringes can be processed.
- NMR can be used to separate the signals from liquid and solid components. This can be used to determine the moisture content in solids, e.g., as a quality check for freeze-dried products.
- The relaxation times of a sample also are dependent on the viscosity of a sample. This means that NMR can detect apparent changes in the viscosity of suspensions due to settling.
- The presence of Ferro-magnetic particles (present in all stainless steel product contact parts) leads to a local field in-homogeneity. The FID response will decay much faster, and therefore, contaminants can be detected by comparing the observed with reference measurements.

Some Remarks on Safety

Some people might associate the application of NMR with large laboratory devices applying large superconducting magnets and high magnetic fields. Alternatively, one may tend to think in terms of the clinical application for Magnetic Resonance Imaging (MRI). Clearly, metal objects like screw drivers and tools experience an attractive force by magnetic fields associated with NMR. Therefore, also electronic equipment like hard disks, credit cards, and people carrying medical implants or cardiac pacemakers in particular are potentially in danger.

In order to reduce this risk, the field outside the NCCW has to be kept at a minimum. According to safety regulations, magnetic fields lower than 5 G (0.5 mT) are considered safe especially for pacemakers. The design of the current NCCW

ensures that the 5 G (0.5 mT) line is well within the isolator. In case of maintenance and service within the NCCW, the field to which extremities are exposed to will exceed the 5 G limit. European and US-regulations clearly set mean values for the maximum permissible exposure of public and operators to magnetic fields. For the so-called 'passive exposure,' e.g. by passers by, the mean value over eight hours is limited to 68 mT (680 G). The max. mean value for operators and service personnel is limited to 212 mT (2120 G). In case of operators of the NCCW, these values will not be exceeded during regular operation. Service personnel has to be well trained and educated to a safe mode of operation also regarding minimal exposure time.

In sum, the NCCW constitutes a safe check-weighing device, because by the design the potential risks that magnetic field exhibit are effectively minimized.

Conclusion

It has been demonstrated that NMR can be utilized to precisely determine the mass of a sample within a vial (referred to as NCCW). In the pharmaceutical industry, the NCCW system can be an integral part of a filling line for pharmaceutical products and can weigh each sample without compromising throughput. The NCCW technique can be applied to both liquid and solid pharmaceuticals.

These features align NCCW with the PAT initiative of the FDA since the 100% check-weighing provides an unparalleled feedback tool to optimize the filling process and to secure quality.

Appendix: NMR in a Nutshell

In a classical picture, NMR can be compared with the behavior of mechanical spinners, which can be described by considering the force field to which they are subjected. Most nuclei possess a non-zero spin (they possess a magnetic moment), which sum to the net magnetization vector \mathbf{M}_0 ($\mathbf{M}_0 = \mathbf{M}(t=0)$) of a macroscopic sample. According to classical electromagnetism, this magnetic moment experiences a torque in a magnetic field $\mathbf{B}(t)$, which leads to the following equation of motion (also known as the Bloch equation):

$$d\mathbf{M}(t) / dt = \gamma \mathbf{M}_0 \times \mathbf{B}(t)$$

γ , the gyromagnetic ratio, is a natural constant for each isotope and maximum for ^1H . This equation of motion describes a precession characterized by a frequency $\omega_0 = -\gamma \mathbf{B}_0$, the Larmor frequency. In the static case, $\mathbf{B}(t) = \mathbf{B}_0$, the magnetization points along the field direction, the longitudinal axis. This is referred to as the equilibrium condition, i.e., all components of \mathbf{M} perpendicular to the field axis, M_x and M_y (in the transverse plane) are zero.

It is clear from the equation of motion and from the analogy to the mechanical spinning top that the system can be forced out of its equilibrium state. In NMR, this can be done by applying radio-frequency (rf) pulse(s); the frequency

of which has to match the Larmor frequency (known as the resonance condition) in order to precess the magnetization. Common frequencies in NMR are several kHz up to 900 MHz, corresponding to fields from earth's magnetic field strength up to about 21 T.

Such a non-equilibrium state has to decay back to the equilibrium state by various relaxation processes (in case of a mechanical spinning top friction forces eventually lead to a relaxation of the rotation). In NMR, these destructive processes are sample-dependent. Depending on the microscopic origin, two types of relaxation processes are differentiated: transverse relaxation T_2 , T_{2e} or T_2^* and longitudinal relaxation, T_1 (also called spin-lattice relaxation). Including these relaxation processes into the equation of motion leads to the phenomenological description of NMR:

$$d\mathbf{M}(t) / dt = \gamma \mathbf{M}_0 \times \mathbf{B}(t) - (M_x \mathbf{e}_x + M_y \mathbf{e}_y) / T_2 - \mathbf{e}_z (M_z - M_0) / T_1$$

Where \mathbf{e}_i are the unity vectors of a right-hand coordinate system. The simplest NMR experiment is a Free Induction Decay (FID) experiment: application of a single excitation pulse at resonant frequency will turn the equilibrium magnetization by 90° into the transverse plane. Following this, the none-equilibrium magnetization will evolve 'freely' under the presence of the static magnetic field, \mathbf{B}_0 (free induction) and will eventually decay back to its equilibrium value along \mathbf{B}_0 - *Figures 1 and 3*.

Once the magnetization \mathbf{M} is in a non-equilibrium state, its transverse components, M_x or M_y , are non-zero and oscillating with time, t . Detection occurs via the induction principle: a time dependent magnetic field will induce a current in a coil. Since a resonance circuit (the NMR probe) is needed to apply the rf pulses to the sample for excitation, the same circuit can be used for detection of the voltage induced due to the time-dependent magnetization.

The simple classical picture outlined above is incomplete since molecular interaction and molecular mobility time scales have to be considered in order to describe the NMR response of a complex material. Considering this variety of effects influencing the NMR response of a spin system, dedicated NMR sequences of rf pulses can be designed. Depending on the question to be addressed by NMR, dedicated experimental schemes can be chosen out of a pool of well-known sequences.

An important fact is the possibility of partially refocusing an apparently decayed magnetization. This principle is used in the NCCW of solids, opening a possibility for signal/noise improvement. The underlying principle can be found in E.D. Ostroff and J.S. Waugh, *Physical Review Letters*, Vol 16, Number 24, 13 June 1966, "Multiple Spin Echoes and Spin Locking in Solids." For an introduction into NMR, the reader is referred to the pertinent NMR literature, for example: E. Fukushima, S. B.W. Roeder: "Experimental Pulse NMR; A Nuts and Bolts Approach," Addison-Wesley Publishing company, Inc. 1981.

Abbreviations

FDA	US Food and Drug Administration
FID	Free Induction Decay
MRI	Magnetic Resonance Imaging
NCCW	Non-Contact Check-Weighing
NIR	Near-InfraRed spectroscopy
NMR	Nuclear Magnetic Resonance
PAT	Process Analytical Technology
VPM	Vials Per Minute

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This article presents a strategic approach to implementing RFID technology to ensure greater consumer safety.

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Reaping the Long-Term Benefits of Integrating Radio Frequency Identification (RFID) into Pharmaceutical Manufacturing

by Vivek Bapat and Glenn Restivo

Whether you believe, as many do, that RFID technology will change the world as much as the personal computer and the Internet, there's no denying that RFID will forever change pharmaceutical manufacturing and distributing as previously practiced. In fact, the change has already begun. Consider the following major RFID-related developments in just the last year:

- In February 2004, the U.S. Food and Drug Administration (FDA) published the report, "Combating Counterfeit Drugs," which recommended that RFID technology be widely used throughout the pharmaceutical industry by 2007.¹ Through this report, the FDA clearly intended to accelerate already-growing pharmaceutical industry interest in testing and developing RFID technology in such areas as RFID standard-setting and technological applied research.
- In the summer of 2004, a group of leading pharmaceutical manufacturers, distributors, retailers, and technology vendors – in a program called Jump Start – completed the first real-world test using RFID technology as a means of curtailing drug counterfeiting. Based on an eight-week test using RFID to ship, track, and trace 13,500 packages of oral solid dosage pharmaceuticals, Jump Start participants learned that RFID can increase product security and patient safety, speed drug recalls and returns, facilitate better order accuracy, and improve labor productivity.
- By the end of 2004, Pfizer, GlaxoSmithKline, and Purdue Pharma announced plans to implement RFID tagging as quickly as possible. Pfizer said it plans to begin RFID tagging of Viagra® by year-end 2005. GlaxoSmithKline wants to apply RFID tags to at least one of its most counterfeit-susceptible products within the next few months. And Purdue Pharma, which is already applying RFID tags to its popular painkiller, OxyContin®, also plans to do so with its newest painkiller, Palladone™.
- In January 2005, most (though not all) of Wal-Mart's top 100 suppliers had at least minimally complied with the retailing behemoth's now-infamous 2003 ultimatum to suppliers to have a system in place for attaching RFID tags to products shipped to Wal-Mart's distribution centers in Texas. Though Wal-Mart's RFID deadline was not wholly met, industry analysts still credit the retailer for being among the first to at least jump-start interest among manufacturers and distributors in applying and using RFID technology. For instance, Wal-Mart's mandate that all Class II narcotics sold in Wal-Mart's retail pharmacies be RFID-tagged led to Purdue Pharma's decision to tag its popular painkillers.

No More Wait and See

Although RFID technology has been around for decades, many industries and companies (particularly those that deal in low-margin products) adopted a "wait-and-see" attitude in recent years toward using RFID. And based on

Radio Frequency Identification

the minimalist approach of some companies to comply with Wal-Mart's 2005 RFID mandate, it will still be a while before RFID technology is widely adopted across the entire wholesale and retail sector.

But for pharmaceutical manufacturers and distributors, the time has clearly arrived for RFID technology. As the FDA has already noted, one of the most critical and timely uses for RFID is its ability to help detect and deter the growing use of counterfeit drugs, which will in turn mean a safer drug supply for consumers. Yet, RFID also will be instrumental for pharmaceutical companies to more easily and rapidly conduct drug recalls, manage inventory, identify theft and/or diverted shipments, and even more readily comply with Section 404 of the Sarbanes-Oxley Act, which requires public companies to report where their goods are located in the supply chain.

In the November 2004 Compliance Policy Guide, "Radiofrequency Identification Feasibility Studies and Pilot Programs for Drugs," the FDA calls out requirements for record-keeping, lot tracking and genealogy, and material tracking and tracing, all of which apply to such regulations as the Bioterrorism Act and 21 CFR Part 211 for finished pharmaceuticals.² Ultimately, as is clear in this and other FDA publications concerning RFID, the FDA views RFID as

an ideal means for identifying and tracking lots and materials through unit operations in manufacturing and across the entire supply chain.

Counterfeiting and product shrinkage are the most immediate concerns among drug manufacturers and distributors. According to industry estimates, between two to seven percent of the world's pharmaceutical drug supply is counterfeit, costing the drug industry approximately \$30 billion annually. And, up to another \$40 billion in pharmaceutical drugs is lost or stolen worldwide each year.³

While drug counterfeiting has long been a problem in nations lacking sufficient regulatory and enforcement measures, counterfeiting is increasingly becoming a problem even in the United States. In the late 1990s, the FDA conducted an average of five full-scale investigations of counterfeit drugs per year. Today, that figure has quadrupled to more than 20 investigations per year.⁴

Among pharmaceutical manufacturers we've spoken with, there's universal concern about the potential consequences to a company's finances and reputation if a healthcare crisis were to unfold involving the counterfeiting of a major pharmaceutical drug. That's why companies such as Pfizer are pursuing RFID so aggressively - to preserve the integrity of

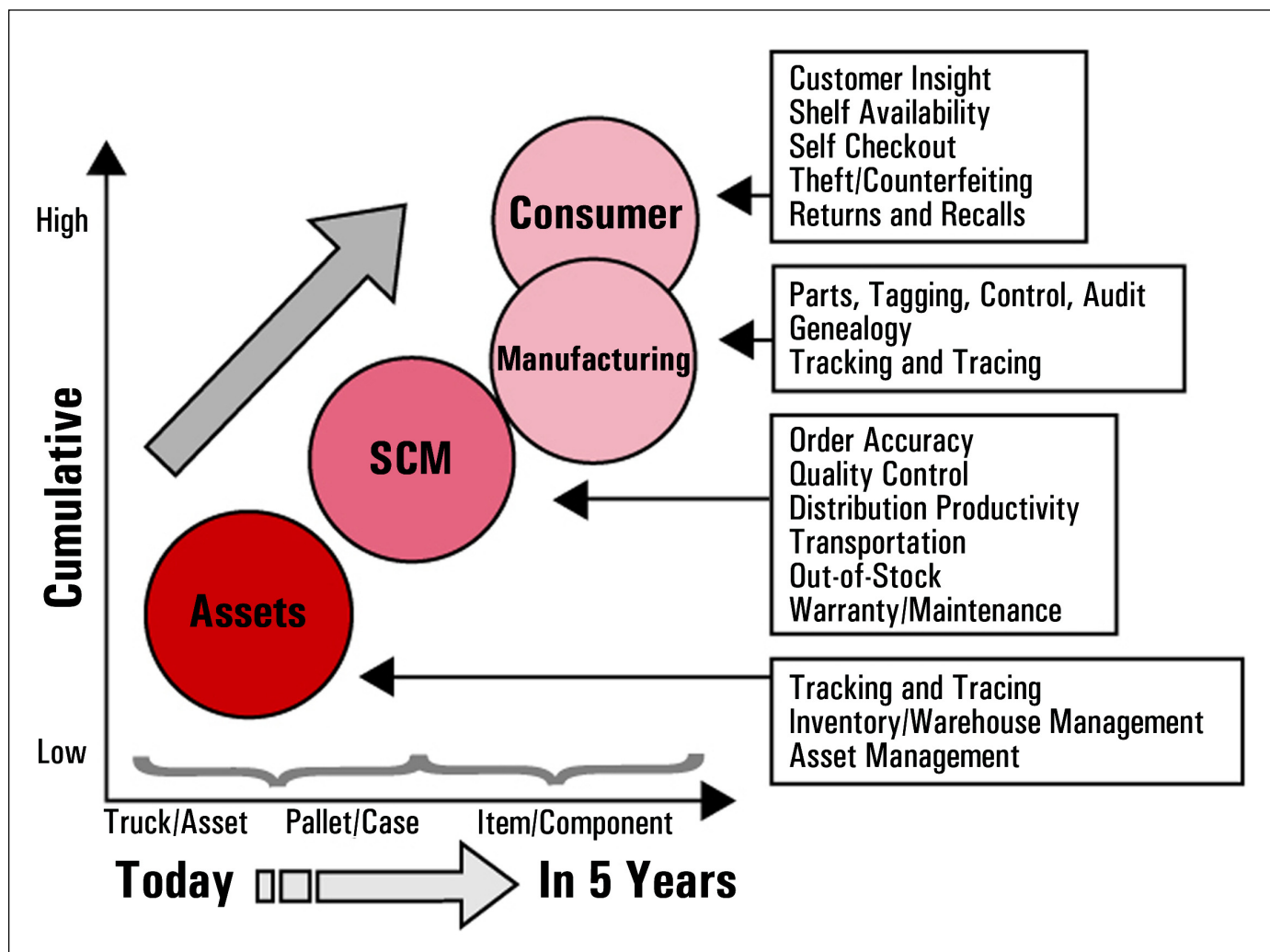


Figure 1. Phase I and Phase II of the RFID adoption cycle.

its flagship brands and better protect the public's health.

Significant Economic Gain

Considering the potential health and economic consequences of a major drug counterfeiting crisis, it's no wonder the FDA is gung-ho about adopting RFID technology - to the point that the FDA is allowing the pharmaceutical industry to at least initially sort out its own RFID standards. Yet, additionally, as many pharmaceutical companies are learning, there are significant financial benefits to be gained by adopting RFID technology, as highlighted in a November 2004 report from the Healthcare Distribution Management Association (HDMA) Healthcare Foundation.

According to the HDMA report, entitled "Adopting EPC in Healthcare: Costs and Benefits," pharmaceutical manufacturers stand to gain between \$500 million and \$1 billion annually by adopting RFID and Electronic Product Code (EPC) technology.⁵ Additionally, healthcare distributors stand to reap between \$200 million to \$400 million annually. Other key findings of the report include:

- Estimated annual benefits to a manufacturer of a \$1 billion drug total up to one to two percent of revenues, depending on the characteristics of the drug.
- Estimated annual benefits to a distributor with \$10 billion in sales can be as high as \$15.5 million annually.
- One-time start-up costs for EPC/RFID integration, hardware, tags, and data processing software range between \$15 million to \$20 million for a large manufacturer.
- One-time start-up costs for EPC/RFID integrations, hardware, tags, and data processing software range between \$9 million to \$20 million for a large distributor.

The HDMA report recommended that the first prescription drugs to be RFID-tagged include those with a high risk of counterfeiting, a high rate of chargebacks, special regulatory requirements, and/or high per-unit sales costs. Next, in terms of tagging priority, should be drugs with high- to medium-dollar values and drugs that have special handling and storage needs.

Before the pharmaceutical industry can widely adopt EPC/RFID technology, the HDMA report noted that the industry must first establish a clear adoption path, create data access and sharing standards among companies, develop interoperable technology standards, find a reliable (and inexpensive) supply of tags, and improve RFID's read-reliability rates.

To meet these and many other issues involving RFID technology, manufacturers and distributors - pharmaceutical and otherwise - are turning for help to an array of companies involved in making and/or providing RFID software, hardware, tags, and consulting services. According to research firm Venture Development Corp, RFID-related revenue will jump from approximately \$1.5 billion in 2004 to

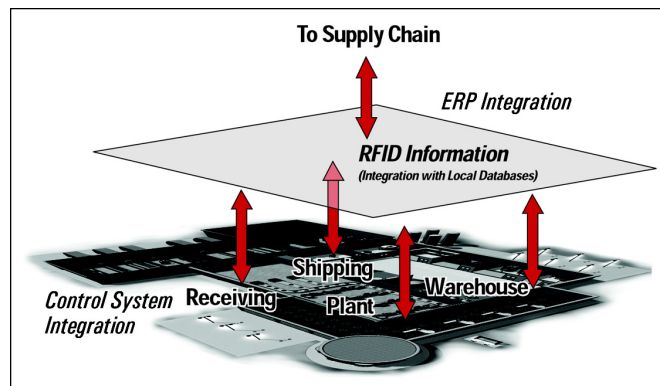


Figure 2. RFID at the plant level.

\$4.6 billion in 2007.⁶ Yet, as companies in the early stages of RFID development are discovering, the ultimate success in using RFID will not come from the technology alone, but rather by how it's integrated with a company's enterprise systems and the business processes that support a company's operations.

Tag, You're (Not) It

Because of the generally higher per-unit values of the products that they make and distribute, pharmaceutical manufacturers and distributors have the luxury of not being as cost-centric about RFID technology (particularly tag costs) as consumer product companies. While tag costs are certainly critical, they should not be the singular focus of companies that wish to glean the maximum Return On Investment (ROI) from RFID technology.

Additionally, pharmaceutical companies cannot look at RFID from a purely traditional ROI perspective - after all, consider the potential economic consequences of *not* applying RFID technology to a single blockbuster drug whose credibility and sales are compromised due to widespread counterfeiting. As detailed in a recent cover story in *RFID Journal*, Purdue Pharma decided not only to comply with the Wal-Mart mandate (to tag individual bottles of Schedule II narcotics), but also to integrate RFID into the company's OxyContin production line.⁷

Purdue Pharma did so knowing there would be minimal ROI in the near-term. But as told by David Richiger, Executive Director of Package Design and Development for Purdue Pharma: "Long-term, we think RFID is the right approach for product authentication and creation of an electronic pedigree through the supply chain. There are significant benefits in our industry to identifying product from the point of manufacture to the retail pharmacy. And we're very interested in working with the wholesalers and retailers to make the information visible up and down the supply chain."

To illustrate how pharmaceutical manufacturers and distributors should likely *not* approach RFID deployment, look no further than the bare-bones approach that several companies took to comply with Wal-Mart's RFID mandate. A study by consulting firm Incucomm found that Wal-Mart's top 100 suppliers and 37 other suppliers spent far less than expected on RFID compliance to meet the mandate - an average of

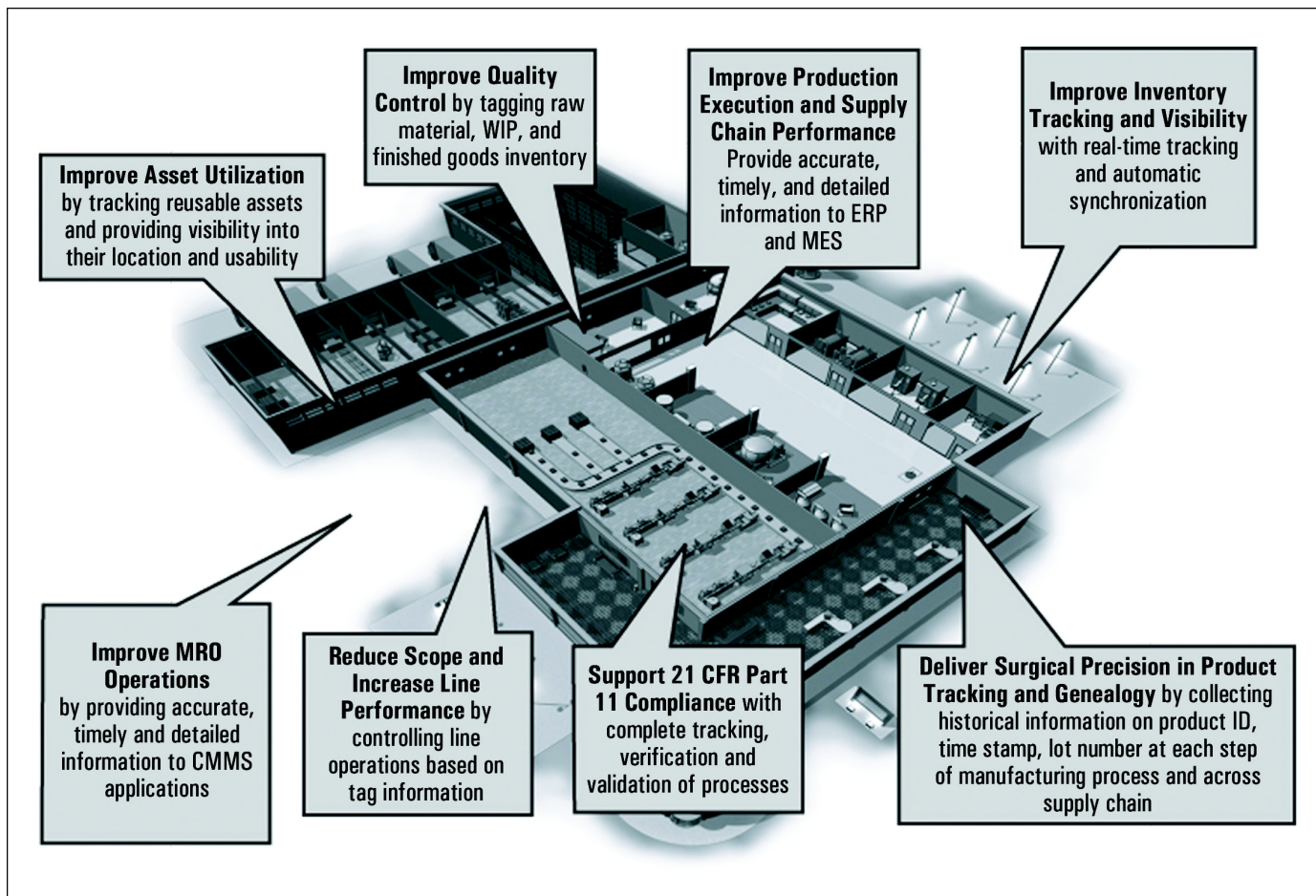


Figure 3. RFID benefits.

\$500,000 each.⁸ It's no wonder that many suppliers struggled to meet the Wal-Mart deadline.

According to the Incucomm study, nearly half the suppliers took a Do-It-Yourself (DIY) approach to comply with Wal-Mart's RFID requirements. The report identified three main reasons for the DIY mindset: the suppliers had insufficient budgets in 2004 for RFID technology; they had already planned to curtail costs (and boost internal knowledge) by keeping the RFID work in-house; or they simply did not know where to turn for help with their RFID and logistics needs. Additionally, nearly one-fourth (24 percent) of Wal-Mart's suppliers took a slap-and-ship approach toward meeting the RFID requirements, meaning that they applied RFID tags to pallets and cases of their products with little or no integration into their IT systems.

By contrast, consider the learning success of 2004's Jump Start initiative among the leading pharmaceutical-related companies. Through Jump Start, not only did participants better realize the intrinsic safety and compliance value of adopting RFID technology, they also learned how and where RFID can boost the bottom line.

For example, by being better able to forecast product demand in real time through RFID, companies can improve their performance across their entire supply network. Across industry, companies with better demand forecast accuracy have 15 percent less inventory, 17 percent better perfect

order ratings, and 35 percent shorter cash-to-cash cycle times than their peers, according to benchmarking studies from AMR Research. Not so coincidentally, these same companies also lead their industries in bottom-line financial and market performance.⁹

The RFID Adoption Cycle

Although companies can gain significant business value by deploying RFID technology, a supplier can't simply slap a smart label - one with an RFID tag embedded in it - on 60 cases, stack the cases randomly on a pallet, and expect to accurately read every tag as a forklift carries the pallet through a dock door at five miles per hour.

Suppliers must resolve several production-related issues before an RFID-tagged product even hits the dock door. For example, products with high liquid content or containing metal (in the product or its packaging) require special consideration since liquids and metals can distort or impede RFID radio waves. Potential solutions might include using a specific type of tag, placing the tag in a precise location on the case, or arranging the cases in a special configuration on a pallet. Many companies are learning through trial and error. It reportedly took the Jump Start coalition two weeks just to determine the right type of adhesive to use to apply the RFID tags in its pilot program.

According to several industry analyst groups, the RFID

adoption cycle for most manufacturers typically progresses from pallet-level tagging to tagging individual products - *Figure 1*. Pharmaceutical manufacturers differ slightly due to their higher inclination to adopt product-level tagging. Leading manufacturers are quickly investigating and adopting RFID initiatives from both short-term and long-term strategic perspectives. This is being accomplished in a two-phased approach, summarized as follows:

Phase I: Tag Application

This phase predominantly consists of closed-loop piloting activity that is internally managed through pilot teams consisting of engineering, warehousing, IT, and plant managers. The goals are to:

- meet the mandates of retailers (such as Wal-Mart) with an impact on post-production, repackaging processes, and the supply chain
- identify integration components into the supply chain that result in minimal impact on current production operations
- select a few product SKUs for piloting purposes
- build a broad business case and strategy for broader RFID integration across the enterprise

Phase I activity examples include devising solutions that trace products at the pallet level and matching the information to a production order. For manufacturers, the main issues in this phase revolve around validating tags, checking errors, and comparing the reliability standards of RFID to those of bar code technology.

Phase II: RFID Deployed as an Integral Part of Operations and to Gain Strategic Advantage

This phase includes tactical and execution plans surrounding increasing levels of integration of RFID deployment into mainstream business operations. As part of this phase, manufacturers ask key questions such as:

- How far downstream into manufacturing and out into the supply chain should RFID be implemented?
- How far upstream and at what level of granularity and into the production process should RFID be implemented?
- Which types of standards, software, and integration should be deployed?

The Wal-Mart RFID mandate was significant to all manufacturers because it meant its top suppliers not only had to put tags on pallets and cases, but they also had to install RFID readers in their manufacturing facilities, warehouses, and distribution centers. The suppliers, in turn, can require their suppliers to tag shipments, a requirement that is then passed on throughout the supply chain. As more and more suppliers adopt RFID, these actions will eventually drive down the cost of tags and readers and encourage still more companies to comply.

This sort of ripple effect was anticipated by leading industry analysts, who now predict that RFID use at the pallet and

case level will increase rapidly due to what economists call the “network effect,” which means that the more people use a physical network (say, the Internet) or shared service (like eBay), the more valuable it becomes. That encourages even more people to use the network, creating exponential growth.

The Impact of RFID on Manufacturing

For years, manufacturers have invested in ways to link production with supply chain information to not only optimize inventory, but also to improve production efficiency, flexibility, and responsiveness. Thanks to new-generation Manufacturing Execution Systems (MES), companies now have a better way to obtain accurate, detailed, and timely information about their manufacturing operations and get the most value out of their existing automation investments.

Yet, for a broad cross-section of manufacturers that haven't made substantial investments in MES, RFID technology potentially provides a means to close some functional gaps, such as those related to tracking and genealogy and compliance management - all of which are issues of particular importance to pharmaceutical manufacturers. For these manufacturers, a combination of RFID investments and incremental, but functionally focused, MES applications can quickly and cost-effectively deliver functionality that parallels comprehensive MES solutions.

For optimal RFID success, efforts to improve inventory visibility across the supply chain should be closely tied to a company's control systems and execution processes driving production. In order to justify the Return On Investment (ROI) of RFID technology, many manufacturers believe that the plant floor presents a vast, untapped opportunity for value creation and even strategic advantage, as RFID moves upstream from the supply chain and into the heart of manufacturing operations.

By applying RFID technology incrementally across the plant floor, manufacturers can seamlessly integrate the new information captured by RFID, without disruption, into existing, proven, industrially hardened control, visualization and information infrastructure, reducing the need for purchasing new infrastructure or investing in expensive, time-consuming, and unproven IT integration projects. Existing manufacturing execution and information systems can then be updated to deliver robust and reliable real-time information flow to drive manufacturing execution in tune with the RFID-enabled supply chain.

An Accenture white paper, “Auto-ID on the Line: The Value of Auto-ID Technology in Manufacturing,” describes in detail the potential opportunities to leverage RFID on the plant floor.¹⁰ The key areas that will be immediately impacted as a result of RFID initiatives include: 1) manufacturing information management; 2) manufacturing execution, quality control, and compliance; 3) tracking and genealogy; 4) plant asset management; 5) inventory visibility; and 6) labor usage. Let's more closely examine each area.

1. Manufacturing Information Management

By combining RFID with existing manufacturing informa-

tion systems that drive both MES and ERP, manufacturers can create a much more potent information supply to drive production efficiencies and improve asset utilization, production quality, and other production measures.

RFID readers will capture the data, but companies still need middleware to process the data and feed it to their enterprise systems. Software manufacturers are now providing completely new middleware software and technologies to provide dynamic near-real-time communication between readers and software using the Internet or other networked platforms.

In order to deliver information from RFID upstream out to the supply chain and Enterprise Resource Planning (ERP) system and downstream into production and the Manufacturing Execution System (MES), companies must convert their existing information infrastructure so that it co-exists with emerging EPC standards and IT, including software and application management technology, such as device brokers.

Once a company can share this information across the enterprise and plant floor, it also must coordinate receiving, manufacturing, warehousing, and shipping operations. Regardless of how much time and money a company spends on RFID at the enterprise level, if it manages and executes RFID poorly at the plant level, many potential RFID-related benefits will be wasted - *Figure 2*.

Manufacturers are increasingly learning the importance of designing and integrating RFID information and solving connectivity issues related to plant floor and warehousing execution so that the new information is integrated into the plant floor reliably and through industrially hardened conduits. An RFID network will be of little or no value to a manufacturer unless the manufacturer can access and manage the information provided using an array of hardware and software that has been brought together explicitly for that purpose and tied back into the plant for execution and action.

2. Manufacturing Execution, Quality Control, and Compliance

RFID has the potential to complement MES by providing new streams of real-time data that can support existing Lean and Six-Sigma programs. Manufacturers can use the RFID information to ensure that the correct labor, machine, tooling, and components are available and ready to use at each processing step, thereby eliminating paperwork and reducing downtime. Furthermore, via RFID data, manufacturers can control, modify, and even reconfigure their process steps in real-time as inbound materials and assemblies move through manufacturing.

For example, a pharmaceutical manufacturer could use RFID technology to tag raw materials with detailed specification information. If a formulation is incorrect, an alert would automatically be triggered. This can help reduce scrap rates and increase yield, assuring a high degree of reliability and quality in processing.

For manufacturing operations that require a high degree of compliance with governmental standards and regulations, such as pharmaceutical manufacturing, RFID can provide

additional information streams to support existing MES activities and enable tighter tracking, verification, and validation of processes.

Can RFID be applicable to Process Analytical Technology (PAT)? The answer is yes, if a company is using the tag information to better understand its processes for quality and continuous verification, as well as demonstrate process understanding and control to the FDA. Using RFID tags as content identifiers adds real time data, and appending this with process information throughout the manufacturing process allows PAT and RFID data to be tied into the process batch record and product release. Through continuous real-time quality verification, a company can reduce quarantine and achieve release by exception.

3. Tracking and Genealogy

As pharmaceutical manufacturers know, increasingly demanding FDA quality requirements are forcing companies to better manage product information, lot tracking, and related quality standards across their entire supply chain network. If a company ever needs to recall a product, it must be done as quickly and as precisely as possible. RFID's ability to provide reliable, accurate, and up-to-date information is absolutely critical to cost-effectively achieving a company's recall objectives.

For manufacturing operations in a pharmaceutical environment that require a high degree of compliance with governmental standards and regulations, RFID can provide additional information streams. In turn, these can support existing MES activities and enable companies to more tightly track, verify, and validate their processes in accordance with 21 CFR Part 11 compliance.

RFID also can complement existing MES efforts to provide genealogy tracking. Typically, at each stage of processing, MES is already collecting information such as product IDs, time stamps, physical attributes, machine and order numbers, and lot numbers. Manufacturers can encode this information onto an RFID tag, pass it downstream to the warehouse at a pallet level, and then out into the supply chain, greatly improving the ability of the manufacturer to re-trace steps in the event of a product recall.

Because introducing the new technology within an existing process requires levels of testing commensurate with risk, a good starting point for customers interested in adding RFID technology is the GAMP 4 model.¹¹ Developing qualification protocols (such as IQ, OQ, PQ) should take into account requirements and specifications as defined by User Requirement Specification (URS), Functional Specification (FS), and Design Specification (DS).

A company implementing RFID should capture its validation process in the validation master plan. Formally commissioning a system requires written specifications and the results of the execution should go through a formal approval process.

4. Plant Asset Management

By using RFID technology to tag their physical assets, such

as machines, fork trucks, and material handling devices, manufacturers can gain better information about the location, usability, maintenance requirements, and contents of these assets. Based on this information, manufacturers can devise production steps as well as maintenance and labor schedules to help increase asset costs, optimize asset performance, and maximize asset utilization.

5. Inventory Visibility

To achieve true supply chain synchronization, manufacturers that rely on contract manufacturing must gain greater visibility into their suppliers, as well as their customers. The better a manufacturer can collect, manage, and use information to drive production assets and processes, the more visibility it can provide to its trading partners.

Depending upon their investments in automation and MES, manufacturers can use RFID in varying scales, either locally or across the entire facility, to provide visibility about incoming raw materials, work in process, production sequencing, packaging, palletizing, and warehousing operations, as well as final shipping.

6. Labor Usage

Bar coding is the current identification standard used in most manufacturing operations, but it typically requires manual intervention, which is costly and time-consuming. Companies that use RFID technology can eliminate their bar coding systems, and thereby free up labor to perform other, more value-added tasks. RFID also can provide more accurate and reliable data than what's available through manual bar coding methods, which can have a major impact in high-volume and high-speed manufacturing operations where speed, accuracy, and timeliness are critical for throughput and performance.

As shown in the chart (Figure 3), RFID can dramatically impact critical performance issues, including machine performance, line performance, plant performance, and ultimately, supply chain performance.

Creating Value through RFID Deployment

As noted earlier, success with RFID will come not through the technology itself, but rather through the ability of a manufacturer to filter and capitalize on its RFID data. Manufacturers will need to enhance their manufacturing information systems to enable them to react to the real-time data provided by RFID, whether it's a sudden spike in demand or a glitch on the assembly line. They also will need to change their business processes and train people to use the data that will be at their disposal.

While there are many hardware, software, and consulting companies that offer RFID equipment and knowledge, very few can provide the comprehensive shop floor to top floor view of RFID that major pharmaceutical manufacturers will require to succeed. RFID is not a simple, plug-and-play technology. Given the complexity of implementing RFID in a manufacturing environment, companies that don't choose the right strategic partner to deploy this technology correctly will

likely finish at a severe competitive disadvantage.

To help manufacturers understand how to determine the best path toward full-scale integration and implementation of RFID technology in their operations, Rockwell Automation has produced a white paper on the subject: "RFID in Manufacturing."¹² The white paper, available at <http://rockwellautomation.com/rfid> illustrates a four-step methodology to approaching RFID in manufacturing, as follows:

1. Business Case Justification and ROI Analysis

This first step includes helping a manufacturer develop a complete ROI analysis to support budgetary needs and investment outlays across the entire supply chain. (As shown in the Incucomm study of Wal-Mart's suppliers, several suppliers struggled to simply justify enough budget assistance to successfully implement RFID in their operations.) The ROI analysis will address numerous business issues: Where will the production and service disruption be minimal, but the returns the fastest? What incremental investments will be needed as part of a long-term strategy, and during what time frame? What's the IT strategy for a full-scale rollout at the MES level?

By conducting simulations and pilot programs, manufacturers can better understand the ROI of their potential RFID investment. For example, through simulation, manufacturers can effectively "test-drive" the deployment of RFID technology within the organization, and under varying conditions and decision criteria, before it is implemented on "live" operations. By using process simulation services and optimization technologies, companies can identify a quick, cost-effective way to realize the real impact of proposed improvements of deploying RFID technology. This helps reduce the risks associated with this capital investment and ultimately helps improve business performance across the entire organization.

Manufacturers can realize the fastest returns on their RFID investments in their end of line and warehousing operations. To help manufacturers better develop and refine these applications, Rockwell Automation has developed an RFID lab and pilot program in Milwaukee, which tests - in real world scenarios - the integration of RFID technology into labor operations, palletizing, conveyor lines, material handling, storage, and robots that facilitate the movement of goods. The lab uses an array of wireless warehouse phased technologies, including wireless LAN, bar codes, and EPC.

2. Design and Architecture

In this step, manufacturers can select tags and readers that are most suited to their environments, provide piloting assistance related to RFID laboratories, set up mobile labs for testing in the customers' environments, and arrange lab tours at existing internal or customer sites. Additionally, manufacturers can design an integration strategy with their existing bar-code implementations and a methodology to integrate their RFID information into their ERP systems, including providing case-to-pallet validation at end-of-line operations.

Another important aspect of this step involves helping manufacturers reliably and cost-effectively synchronize their RFID information with their control systems; help them identify how to coordinate their RFID technology with existing MES implementations, and help design process and automation capabilities to facilitate item-level tracking and tracing functionality.

By participating in the University of Wisconsin's e-Business Consortium RFID Industry Workgroup, users can draw upon the latest and brightest thinking in RFID applications and pass this information along to its customers and prospects (who also often attend the consortium's meetings). The consortium, which includes such diverse companies as Case New Holland, Kohler Company, and Kraft Foods, helps participants better understand the challenges and pitfalls of RFID integration; consortium participants freely share advice on evaluating and installing the latest in RFID technology.

3. Software and Systems Integration

In this step, manufacturers can comprehensively integrate their RFID implementations into mainstream manufacturing and warehousing operation - from the ERP level to the control level. This step also includes custom services, such as software and engineering services that facilitate integration with middleware and integration with local database management systems, ERP systems, control systems, and MES.

4. Maintenance and Support

An RFID project doesn't stop after it is implemented. There is an ongoing process of maintenance and support to ensure that all aspects of the RFID implementation are continuously monitored and supported at an engineering level, as well as from an information service perspective.

Real-World Experience

To better understand the cost and viability of RFID on behalf of its own customers - as well as more efficiently track product distribution and capture shipping data to meet international customs requirements - Rockwell Automation recently created its own successful RFID pilot program. The company is now using RFID to track products originating from its Twinsburg, Ohio, manufacturing plant and sent to its largest distribution facility in Champaign, Ill., which handles more than 20,000 product SKUs.

The 257,000-square-foot Twinsburg plant serves as one of the core manufacturing hubs for the company, and produces more than 1,700 different products, including programmable controllers, input/output (I/O) cards, communication interfaces, and motion controllers. Three serialized products were initially identified for the pilot RFID program.

The RFID program at Twinsburg operates like most RFID processes. Finished products exit the production line and are packaged into a shipping box. Operators then attach a bar code label (which contains a serial number) as well as an RFID tag onto the box. The box is passed under an RFID antenna where the RFID tag ID is read and uploaded into a

database where it is linked with the product ID and serial number.

Upon arriving at the distribution center in Champaign, the RFID tag is read at the dock door, and the product is transferred to a designated area of the warehouse. When the product is picked to fill an order, the bar code is scanned with a handheld reader, and the product is placed onto a conveyor system. At a quality control station, an antenna portal reads the tag and captures the product data, allowing the company to link the serial number and product to a particular order.

The software system purges any tags that are read twice so that the database accurately represents the number of products passing through the system. At the last stage, the product is boxed and shipped to the customer. On an average day, between 50 and 100 RFID-tagged pieces pass through the scanners and are shipped to distributors.

With the availability of RFID-tagged finished goods, the Champaign distribution facility has improved its cycle count efficiency by eliminating piece part counting of the RFID-tagged SKUs. Additionally, the system has automated the transfer of serial numbers that previously required an extra bar code scan. In all, RFID has helped the company improve the visibility, accuracy, and productivity of the company's supply chain - at least involving its RFID-tagged products.

Based on the pilot program's success, plans to use the RFID technology to help track product field warranty data are being evaluated. Several of the company's customers and prospects have toured the Twinsburg and Champaign facilities to get a better understanding of the company's understanding and application of RFID technology.

Summary

For pharmaceutical manufacturers seeking to better manage inventory and more rapidly conduct recalls and reduce counterfeiting, theft, and shrinkage, RFID technology is clearly superior to any other competing alternative. Companies in this industry would be wise to think about the potential benefits of RFID far beyond just an ROI equation; the potential consequences of not applying this technology are too large. Instead, companies should look to and learn from the RFID success examples provided by others within their industry, work incrementally with the right strategic partners to add RFID technology to their own operations, and begin to enjoy the innumerable benefits which RFID technology promises.

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This article discusses cleaning validation vs. cleaning verification in addition to listing the minimum requirements needed prior to performing equipment cleaning processes in Clinical Trial (CT) Manufacturing and Packaging.

Equipment Cleaning in Clinical Trial Material Manufacturing and Packaging

by Matthew Gerber, Deborah Perona, and Lisa Ray

Introduction

Engineers and chemists working in the pharmaceutical industry continually strive to improve upon the processes by which drug products are manufactured and packaged. Part of the process involves the cleaning and maintenance of the equipment used to manufacture and package the products. The FDA outlines the regulations in 21 CFR 211 for the minimum current Good Manufacturing Practices (cGMPs) for the preparation of drug products. The equipment and systems used to manufacture and package drug products are cleaned to prevent equipment malfunctions or contamination of drug products.¹ This article discusses cleaning validation vs. cleaning verification in addition to listing the minimum requirements needed prior to performing equipment cleaning processes in Clinical Trial (CT) Manufacturing and Packaging.

Background and Definitions

Cleaning programs are a routine process in the preparation of CT materials, and are employed to prevent equipment malfunctions or contamination of drug products that could alter the Safety, Identity, Strength, Purity or Quality (SISPQ) of the drug product. There are different types of cleaning programs used to ensure the cleanliness of equipment, depending on several variables. For the purposes of this article, only the terms associated with this case are defined.

A minor clean is a cleaning procedure designed to remove visible residual powder. Disassembly and reassembly may or may not be necessary to perform a minor clean. Cleaning agents are typically not used for a minor clean. An example of when a minor clean is performed is between the packaging of a placebo CT ma-

terial and a CT material containing an active ingredient, provided that both materials contain the same inactive ingredients, or between lots of the same active ingredient provided the next lot is higher in dosage strength.

A major clean consists of removal or disassembly of the equipment, cleaning, washing, and completely drying to avoid contamination of future lots before use in a subsequent operation. Examples of when a major clean is performed include: between CT lots of different active compounds; the next lot scheduled to run is lower in dosage strength or contains different inactive ingredients than the lot currently in progress; or between the manufacture of a placebo and a lot containing an active ingredient in which the CT materials contain different inactive ingredients.

Cleaning swabs (referred to as swabs here forward) are long handled polyester-tipped cleanroom swabs and are used for direct surface sampling or swabbing.

Direct surface sampling is a sampling method used to detect soluble and insoluble residue.

Cleaning Validation vs. Cleaning Verification

A cleaning validation program requires that the following conditions apply:

- The equipment and product mix are well defined.
- The products used in the equipment have a predictable lot size and formulation.
- A robust and repeatable cleaning procedure for the equipment exists.

If cleaning validation applies, it is deemed acceptable to perform a prospective validation for a specific product utilizing an approved

protocol. That is, if three consecutive lots of a product are to be processed, a major clean and direct surface sampling (i.e., swabbing or rinse sampling) is performed after each of the lots. The test data collected from the three consecutive lots is evaluated. If the data is acceptable, it can be assembled into a cleaning validation package and routine monitoring for equipment cleaning is no longer required for that compound.

It also is considered acceptable to select a representative range of similar products and processes and perform cleaning validation. This representative range of similar products is commonly termed “model compounds.” Model compounds can be chosen on the basis of solubility behavior in the cleaning solutions, potency, toxicity, and/or compounds that otherwise pose a unique challenge(s) to the cleaning process. After choosing the model compounds, a modeling approach for testing can be used to confirm that the model compounds are removed after washing and rinsing the equipment. This modeling approach for testing can be done by spiking equipment with a known amount of product that is representative, the equipment can be cleaned, and data from direct surface sampling can be collected. If enough data is gathered and is deemed acceptable, it can be assembled into a cleaning validation package and routine swabbing is no longer required for the products represented by the model compound.

Due to the nature of CT Manufacturing and Packaging, such as unpredictable lot sizes or change in formulations, an alternate approach to cleaning validation (i.e., cleaning verification) also can be used.

Cleaning verification is performed on a piece of equipment if:

- The equipment and product mix are not well defined.
- The products used in the equipment do not have a predictable lot size and formulation.
- A robust and repeatable cleaning procedure for the equipment does not exist.

Cleaning verification consists of routine monitoring of equipment cleaning processes. For example, after a major clean is performed on a piece of equipment, direct surface sampling (i.e., swabbing or rinse sampling) is used to verify the cleanliness of the equipment each time the equipment is used.

Figure 1 outlines the equipment cleaning cycle, including the major and minor clean, direct surface sampling (i.e., swabbing in this case), and swab analysis performed as part of the equipment cleaning verification process.

The cleaning verification program currently utilized at Eli Lilly and Company concentrates on production equipment that comes in contact with the active product. Cross-contamination of this equipment could affect the SIS PQ of the pharmaceutical product.

As shown in Figure 1, following a major clean, equipment cleaned during routine cleaning verification exercises is placed on HOLD until the cleaning acceptance criteria is met and reviewed by quality control. The equipment is then released from HOLD per local procedures. Cleaning verification is not necessary following a minor clean. Verification is deemed ac-

ceptable when the equipment is both visibly clean and it meets the acceptance criteria for active residues, as appropriate.

Requirements for Equipment Cleaning Processes

Whether using cleaning verification or cleaning validation, following are 11 minimum requirements needed for performing equipment cleaning processes in Clinical Trial Manufacturing and Packaging along with implementation options for each requirement. These minimum requirements were established in accordance to the ICH, Q7A Guidelines on Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients, Equipment Cleaning and Maintenance.²

Requirement 1 - Cleaning Procedure: a detailed cleaning procedure including critical cleaning parameters such as cleaning agents (e.g., concentration and quantity), cleaning conditions for washing, rinsing and drying (e.g., water type, time, temperature, volume), and disassembly and reassembly instructions required to perform a manual or automated clean must be clearly defined.

Implementation Option: area specific general equipment cleaning procedures can include all general equipment cleaning requirements such as cleaning agents (e.g., concentration and quantity, cleaning conditions for washing, rinsing and drying (e.g., water type, time, temperature, volume), and detailed instructions for disassembly and reassembly to be followed during equipment cleaning.

Requirement 2 - Visual Clean Process: instructions for conducting and documenting a visual inspection must be defined. Visual inspection provides a rapid assessment of equipment cleanliness and is used to verify that there are no areas within the processing equipment that contain residues that can be seen with the unaided eye. Visual inspections should be conducted on dry equipment and documented appropriately. Procedures should provide instructions on how to document the required visual inspection completed during equipment cleaning. An acceptable visual inspection is a pre-requisite to performing direct surface sampling (i.e., swabbing or rinse sampling) and is performed prior to equipment use. In addition, an acceptable visual inspection can be used as the cleaning verification limit for surfaces with no reasonable possibility of contacting a drug product and for small equipment that can be fully disassembled and fully visually inspected.

Implementation Option: area specific general equipment cleaning procedures can include detailed visual inspection requirements (e.g., visual inspection locations, adequate lighting) and materials needed to perform the visual clean (e.g., flashlight, mirrors, magnification devices). Instructions on how to document the required visual inspection can be dictated by a procedure as well.

Requirement 3 - Sampling Instructions: direct surface sampling (e.g., swabbing or rinse sampling) instructions must be defined. Given the nature of the equipment and the level to which it can be disassembled, direct surface swabbing can be an appropriate sampling technique for assessing equipment cleanliness. In many cases, the analytical labora-

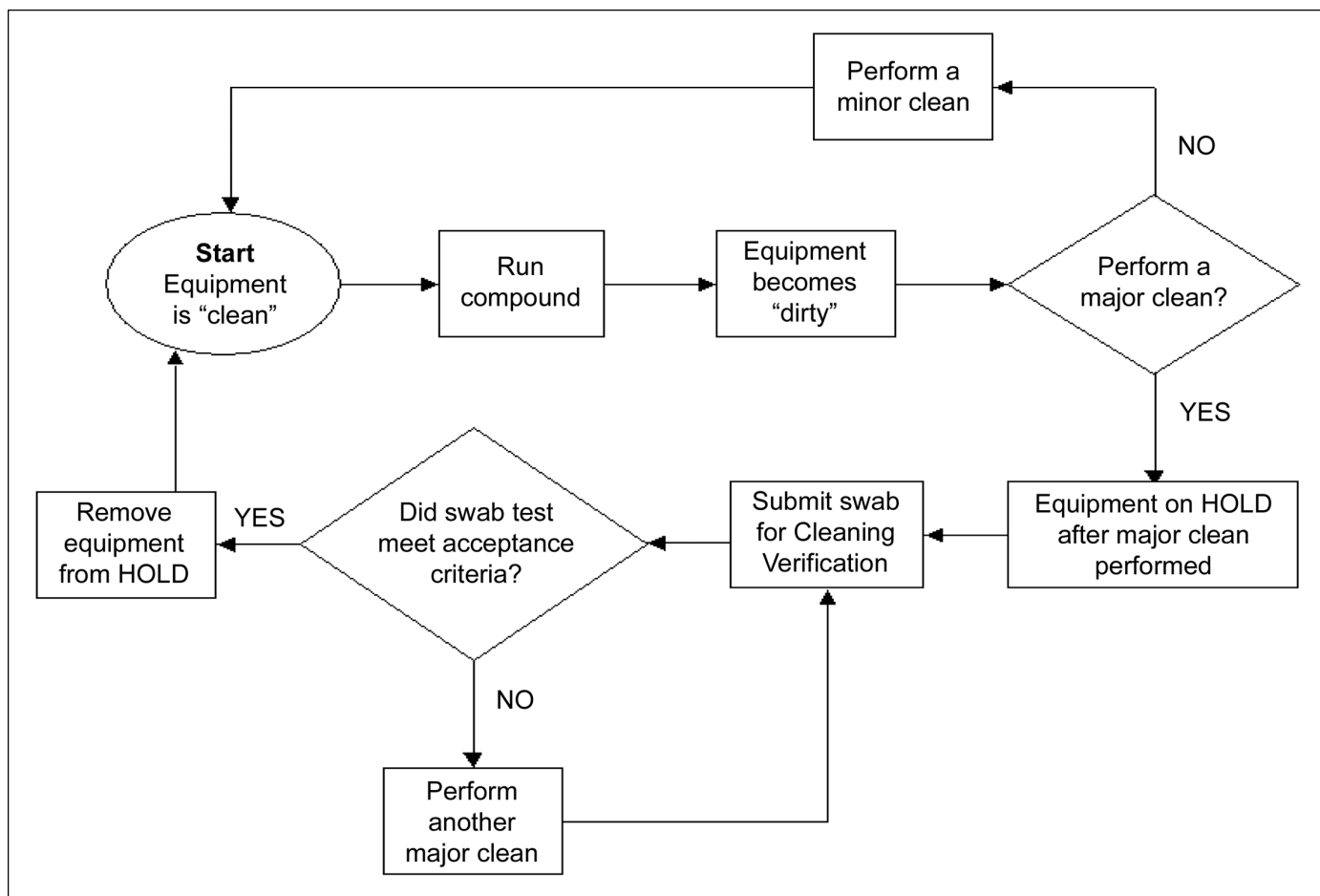


Figure 1. Equipment cleaning cycle.

tory that developed the testing method (i.e., swab testing method or rinse testing method) also will develop the instructions for obtaining the direct surface sample.

Implementation Option: during development and validation of the swab or rinse sampling analytical method, the development scientist should select a suitable solvent for use in direct surface sampling. Any additional instructions on technique for obtaining the sample also should be specified.

Requirement 4 - Maximum Dirty Equipment Hold Times: for validated cleaning processes, a maximum period that equipment can remain dirty must be defined. If cleaning verification is currently being followed, maximum dirty hold times are not required because sampling is always performed.

Implementation Option: while executing cleaning validation, build in a pre-determined dirty hold time. For example, if CT Packaging equipment routinely sits dirty for a known time period, then a longer time period should be represented when executing cleaning validation.

Requirement 5 - Appropriate Equipment Storage: storage practices must be in place that allow for identification and storage of clean versus dirty equipment. Clean equipment must be stored in a manner to prevent contamination. A system must be in place to prevent dirty equipment or equipment waiting for cleaning verification results from being used.

Implementation Option: area specific general equipment

cleaning procedures should include, but are not limited to, the following equipment storage requirements: instructions for protecting clean equipment during storage or transport, designated storage areas, and labeling requirements.

Requirement 6 - Maximum Clean Equipment Hold Times: a maximum time allowed between cleaning and re-use/re-cleaning must be established. A documented pre-process rinse approach may be utilized instead of establishing a specific hold time, when applicable.

Implementation Option: Procedures should provide details around the maximum time allowed between cleaning and re-use/re-cleaning and/or a documented pre-process rinse process that will be defined instead of establishing a specific hold time.

Requirement 7 - Validated Analytical Methods: when performing direct surface sampling, an analytical method for cleaning verification must be available and validated. In addition, product contact surfaces (e.g., material of construction for swab locations) must be considered. If non-specific methods (e.g. Total Organic Carbon, Conductivity) for routine monitoring are used, the methods must be validated and product contact surfaces and product solubility must be considered.

Implementation Option: Material of construction must be determined for all product contact equipment. The material of construction for the product contact equipment used to

Component	Construction Material	Surface Area (% of Total)	Factor	Number of Swabs
Hopper	316 Stainless Steel	30.5	SA, ED, MC	1
Feeding Tray	316 Stainless Steel	37.2	SA, CD	1
Chute Block	Oilon	11.8	MC, CD	1
Product Tube	Acrylic	7.1	MC	1
Chute Cover	Vivak	5.1	MC	1
Chute	316 Stainless Steel	1.5	ED	1
Comparison of the components and the rationale used to determine the swab locations and number of swabs used for each component. Legend for the Factor column is as follows: SA = Surface Area MC = Material of Construction ED = Energy Dissipation CD = Cleaning Difficulty				

Table A. Tablet bottle-filling equipment.

package or manufacture CT materials should be considered in the validation of the analytical methods for cleaning verification.

Requirement 8 - Established Equipment Cleaning Training Program: personnel need specific training prior to performing equipment cleaning related tasks.

Implementation Option: employees should reference their individual training plan to ensure that all courses related to cleaning-related tasks have been completed. In addition, Results Oriented Training can be utilized for personnel involved in equipment cleaning.

Requirement 9 - Established Cleaning Verification Acceptance Limits: defined acceptance limits with supporting rationale must be established and pre-approved by Quality Control.

Implementation Option: the swab test acceptance limits can be calculated by determining the carryover of each product to all of the other products that share a piece of equipment. In order to determine an acceptance limit for the swabs taken from the equipment during the cleaning verification, the calculations are based on the product contact surface area, the strength of the first and subsequent products processed on the equipment, the lot sizes processed, and the maximum dosage being tested in humans. Historical data from lots manufactured and packaged in the CT area can be used to develop the limits.

Requirement 10 - Approved Cleaning Agents: cleaning agents (other than water) for cleaning product contact surfaces must be approved prior to use and a toxicology opinion must be obtained. To ensure that the approved cleaning agents do not themselves contribute a contamination risk, cleaning agent validation packages are required if routine monitoring is not performed.

Implementation Option: Solubility of the product should be considered in the selection of the cleaning agent. In addition, the formulation of the cleaning agent will be documented to ensure that the supplier is contacted annually to confirm no changes in formulation have occurred.

Requirement 11 - Justified Sampling Locations: direct

surface sampling locations (e.g., swab and/or rinse locations) utilized in the equipment cleaning process must be documented and justified.

Implementation Option (including Eli Lilly and Company example): in the CT materials area at Eli Lilly and Company, four major factors are considered for the selection of product contact sampling locations. These factors have been identified as contributors for drug product residues left on manufacturing and packaging equipment after a major clean. One or more of the four major factors can drive the location and number of swabs used during the cleaning program. The decision on the number and location for all swabs is determined by making a justification based on the following four factors: Product Contact Surface Area, Energy Dissipation, Materials of Construction, and Difficulty of Cleaning. A swab location is placed in each of the product contact areas that are impacted by any of the four characteristics.

Finally, a check is built into the engineering process for bringing new equipment into the CT Packaging and Manufacturing areas. This check includes ensuring that all product contact locations on the new piece of equipment are one of the already approved materials of construction that are considered when developing analytical methods used during equipment cleaning. The engineering process also includes measuring and documenting the product contact surface area on equipment and selecting the product contact sampling locations that will be utilized in the equipment cleaning process.

A Case Study

The following case study is included to further describe the scientific justification for sampling locations used in the CT Manufacturing and Packaging at Eli Lilly and Company.

As previously mentioned, four major factors were identified as contributors for drug product residues left on packaging equipment after a major clean. One or more of the four major factors can drive the location and number of swabs used during the cleaning verification program. By developing a scientific justification based on these contributing factors, a determination for the number and location of swabs used on the equipment can be made.

The four major factors utilized at Eli Lilly and Company are as follows:

1. Product Contact Surface Area
2. Energy Dissipation
3. Material of Construction
4. Cleaning Difficulty

Four Major Factors Defined

Product Contact Surface Area

The product contact surface area is one factor used to determine the number of swabs and their locations. Equipment components such as hoppers often contain large surface areas that can increase the amount of contact with the product. This large surface area would therefore require swab analysis for more areas. The exact number of swab locations is

determined from a calculation of the component's surface area. If a component's surface area represents 25 - 75% of the total surface area of the equipment, one swab location will be dedicated to the component. If a component's surface area represents more than 75% of the equipment's total surface area, two swab locations will be dedicated to the component. The ranges indicated in the total surface area were selected as a starting point and will be reevaluated during periodic reviews of the cleaning program.

Energy Dissipation

The next factor, which can determine the location and number of swabs taken from a component, is the energy dissipation of a drug product onto the equipment. By observing equipment operations, it has been determined that a significant factor in the probability of any product breakage is due to a sharp change in the mechanical energy of a capsule or tablet as it travels through the equipment. The energy displacement from the product to the equipment is proportional to the amount of drug product that adheres to the equipment. This can potentially leave residue on the equipment that is difficult to remove during a major clean. Therefore, each area of the equipment exhibiting energy dissipation will be a location for a swab.

Material of Construction

Materials used in the construction of the equipment or substances required for operation are a potential source of residual product.³ Composition and surface properties of the construction material determine the ease at which the equipment can be cleaned as well as the level of product degradation during the drug packaging process. Hence, each material type used in the construction or the operation of the equipment will be a location for a swab.

Cleaning Difficulty

Equipment with tight corners, bends, curves, small clearances between surfaces or surface anomalies represent difficult to clean areas. The residual product or cleaning agent can potentially get trapped in these areas, and may not be removed during the cleaning process. These difficult to clean areas can be determined by experimentation or from experience cleaning the equipment. Each hard to clean area will be a location for a swab.

This case study represents the four factors as applied to bottle-filling equipment in the CT Packaging area.

Product Contact Surface Area for Bottle-Filling Equipment in CT Packaging

The surface areas were calculated for each component and it was determined that two of the bottle-filling equipment components had large surface areas. In this case, the Hopper and the Feeding Tray each represented more than 25%, but less than 75% of the total product contact surface; therefore each of these components required one swab location.

Energy Dissipation for Bottle-Filling Equipment in CT Packaging

Energy dissipation was configured using a qualitative analysis of the tablets' interaction with the equipment's components. Due to the collisions between tablets as they enter each component, the two areas of concern were determined to be the Hopper and the Chute Cover leading the tablets into the bottle. The energy transfer at these locations very often results in particles from the tablet adhering to the surface of the component. Therefore, each of these components received one swab location.

Material of Construction for Bottle-Filling Equipment in CT Packaging

The bottle-filling equipment contained four material types: 316 Stainless Steel, Oilon, Acrylic, and Vivak. Each type of material used in the equipment will be a location for a swab.

Cleaning Difficulty for Bottle Filling Equipment in CT Packaging

The technicians who routinely clean the equipment completed surveys in order to determine the difficult to clean areas. Based on this feedback, the Feeding Tray and Chute Block were determined to be the most difficult areas to clean. Each of these components received one swab location.

Results

Table A shows the scientifically justified swab locations for the bottle-filling equipment. The fourth column of the table shows which factor or factors were used to determine the swab location. Note: if the same swab location can be used to accommodate more than one factor, then the component will only have one swab location. For example, one swab was placed on the Hopper at the point of energy dissipation and will satisfy the large surface area, energy dissipation, and one of the materials of construction.

As the case study shows, it was determined that there were six locations to be swabbed for the bottle-filling equipment. This same scenario is performed for all equipment with product contact areas to determine justified swab locations to be utilized while executing cleaning validation or verification.

Summary

This article outlines key differences between equipment cleaning validation and equipment cleaning verification. It also reveals important requirements to be considered for implementing a sustainable equipment cleaning process and provides a case study specific to justification of sampling locations used in the equipment cleaning process.

The overall objective of any equipment cleaning program is to establish documented evidence that the cleaning process consistently provides a high degree of assurance that, production equipment and systems are free from materials that would contaminate or adulterate subsequent products to the extent that "fit for use" would be compromised. Following the requirements outlined in this article provides a framework for building a successful equipment cleaning program.

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This article discusses the reasons for inerting a mill, what methods to employ to determine if a product is explosive, and the various factors used to define explosibility. It compares inerting to other protection strategies and concludes with a review of the different inerting methods.

Inert Milling Systems

by Ruby Jacobson, P.Eng.

In many of today's pharmaceutical processing plants, a high proportion of process materials assume a powder stage on their journey to the end-product. The uncontrolled handling of these powders during the process period can easily lead to the generation of electrostatic sparks and the risk of fire and explosion. As a result of this risk, inerting is being seriously looked at in order to further increase the safety of both plant personnel and the process line itself. Inerting is the process via which an inert gas is added to a combustible mixture to reduce the concentration of oxygen below the Limiting Oxygen Concentration (LOC). The inert gas is usually nitrogen or carbon dioxide. This article discusses the reasons for inerting a mill, what methods to employ to determine if a product is explosive, and the various factors used to define explosibility. It compares inerting to other protection strategies

and concludes with a review of the different inerting methods.

Why Inert a Mill?

It is important for process engineers to realize that this is a question that must be answered by explosion experts, based on the characteristics of the product being milled and the condition of the product.

According to one professional process safety firm, "for a dust explosion to occur, the dust must be explosible, airborne, be in concentrations within the explosible range, have a particle size distribution capable of propagating flame, an ignition source is present, and the atmosphere must support combustion."¹

Inerting is often chosen for processing explosible powders in mills because it is impossible to remove the ignition source from mills, impossible to reduce the dust concentration,

Figure 1. No oxygen monitoring.

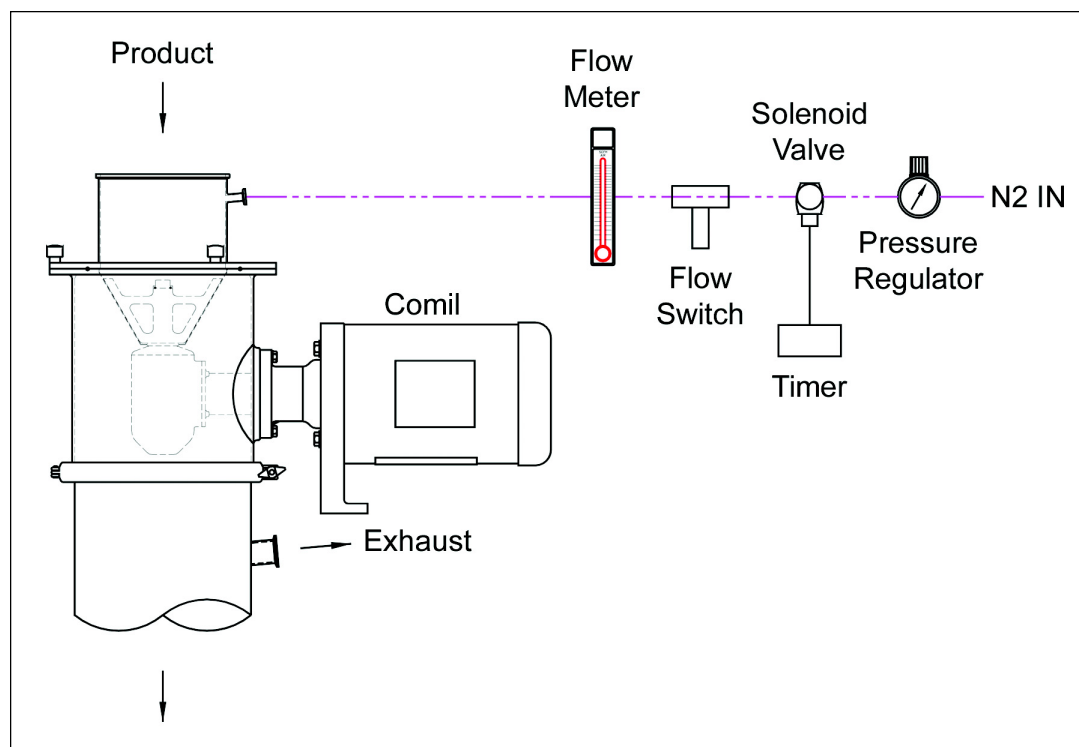




Figure 2. Mobile inert mill system with oxygen monitoring controls.

and generally, costs less than pressure-resistant processes, venting, or suppressant systems.

How do I know if my product is explosive?

Test Method - Dust Bomb

A dust bomb, 20L (0.02m³) test vessel is used to determine whether the dust cloud is explosible as a result of the dust handling/milling conditions. A portion of the powder is injected into the test vessel, dispersed as a cloud by a blast of air, and exposed to an ignition source. Many federal standards such as ISO and ASTM govern the various procedures and dictate the apparatus to be used for these tests. In general, dusts, which ignite and propagate away from the ignition source, are considered “explosible.”

Dusts, which do not propagate flame away from the ignition source, are considered “non-explosible.”² However, non-explosible powders also are known to present a fire hazard and may be explosible at elevated temperatures.

Minimum Ignition Energy (MIE)

MIE of a flammable material is the minimum spark energy (in mJ) needed to ignite a material using a capacitive spark, under specific conditions. The apparatus is a modified dust bomb. An appropriate quantity of dust is placed in the dispersion cup at the bottom of a 1.2L plastic cylinder and dispersed by a blast of air. A spark is discharged across two electrodes located above the powder source. This spark is discharged at the same time as the dust cloud reaches the gap between the two electrodes. Starting with a value of spark

energy that will reliably cause ignition of a given concentration of the dust being tested (note: dust concentration also is a variable), the test energy is successively halved until no ignition occurs during 10 successive tests. Then, starting at a lower energy where ignition does not occur, the energy is increased until an ignition does occur. The MIE is defined to lie between the highest energy at which ignition fails to occur in at least 10 successive attempts in order to ignite the dust/air mixture, and the lowest energy at which ignition occurs within 10 successive attempts. Powders with a MIE of lower than 10 mJ are highly sensitive to ignition. The majority of ignition incidents occur when ignition energy is below 25 mJ. The hazard from electrostatic discharges from dust clouds should be considered.¹

Minimum Ignition Temperature (MIT)

MIT of a dust cloud or of a dust layer is a measure of its sensitivity to ignition by hot surfaces. An example of a laboratory test for MIT of a dust layer is as follows: a layer of dust is placed on a hot-plate and the temperature of the hot plate and the temperature of the dust layer are monitored. Ignition is defined as the point at which there is a significant rise in the dust temperature. The MIT is the lowest hot-plate temperature that can initiate ignition.

It is important to consider the MIT for a milling process because of the potential for heated surfaces in mills if the drive box is in the contact area, and heat is generated from inter-particle friction, screen blinding, or the impact force between the hammers, pins, or particles. A low energy mill, such as a Conical Screen Mill, generates almost no heat during the milling process. However, there are many other types of mills used in industry such as the Pin Mill or Hammermill that generate heat due to the high energy required for milling. The mill supplier would be the best source via which to determine the temperature that a powder would be exposed to, within a mill, under normal operating conditions and also, when something goes wrong. Special designs incorporating cooling jackets may be necessary for some applications/mills.

Limiting Oxidant Concentration (LOC)

The LOC is critical when designing an inert system. It dictates the Maximum Oxygen Content (MOC) allowable within the process area. Wiemann (1989) recommended that the MOC be set at 2-3% lower than the LOC determined by the lab test.²

The LOC is the Oxidant content measured in % volume, below which the product’s dust cloud is unable to propagate a self-sustained flame. The LOC is dependent upon the material and type of inert gas used. Nitrogen is the most commonly used inert gas. Carbon dioxide and Argon also are used. Details regarding the type of inert gas to be used should be provided at time of testing.

The apparatus used for this test is similar to the one used for determining the MIE. However, the cylindrical test chamber where the dust cloud will be dispersed and where the electrodes are located is initially flushed with a specific

concentration of inert gas/oxygen mixture. This same gas mixture also is used to disperse the dust sample into the test chamber tube. After a pre-set delay, a soft spark of approximately 3 J (this may vary depending on the dust) is discharged across the spark gap in the dust cloud within the tube. The test is repeated 20 times at each oxygen concentration. The LOC is basically the highest concentration at which no ignition occurred during 20 trials.

Explosion Severity

The Kst value is often cited in discussions regarding explosible powders. The Kst is a function of the maximum pressure rise during an explosion of a particular powder:

$$K_{st} = (dP/dt)_{max} \times V^{1/3}$$

Where Kst = material constant [bar m/s]

$(dP/dt)_{max}$ = maximum pressure rise [bar/s]

V = volume of the test vessel [m³]

This was derived from theoretical work by Henrich and experimental work by Bartknecht.³

Lab test apparatus varies in size and shape. For example, the dust bomb test consists of a 1.2L cylindrical test chamber with a pressure transducer at the top with which to measure the pressure. The standard ISO vessel consists of a 1m³ sphere equipped with pressure sensors. The Siwek 20L sphere is similar to the ISO sphere, but on a much smaller scale. The dust sample is dispersed as a cloud into the test chamber and ignited to cause an explosion. The dust dispersion method and the igniters also vary from one test method to the next. Some dusts are dispersed from a nozzle; others are dispersed with a perforated ring in the test chamber.

This test provides the Pmax, which is the maximum pressure generated during an explosion. This information is important in the design of a mill if a pressure-resistant process is selected.

Other Tests

There are many other tests that deal with explosive materials and the severity of explosions. Some examples include Minimum Explosion Concentration, Propagating Brush Discharge, Conductivity, Charge Relaxation, Volume Resistivity, and Surface Resistivity. To test for your particular needs, it is recommended that professional process safety firms be contracted.

Inerting Versus Other Protection Strategies - When to Inert?

There are a few options available for processing explosible materials. Basically, there are five strategies that can be employed:

a) Containment: building the entire process train to withstand the Pmax of the explosion.



Figure 3. O₂ sampling panel.

b) Isolation: building critical components (such as a mill) as pressure rated vessels with pressure rated quick shut-off valves for isolating the mill.

c) Suppression: fire retardants are released at the onset of an explosion.

d) Venting: building vent panels on the process train to allow explosions to be directed to an external environment.

e) Inerting: inerting the process train

Suppression involves the use of water, sodium bicarbonate, or mono-ammonium phosphate that is injected at the onset of an explosion and a pressure sensor which monitors internal pressure. Venting is generally used on large, stationary equipment located close to the outside wall.

In our experience, we have found that these two methods have not practically met the needs of pharmaceutical manufacturers. Vent panels also may not be plausible due to size or location constraints. That leaves containment, isolation or inert systems.

Nitrogen costs approximately \$0.02/ft³. This equates to a cost of approximately \$5/hr for a typical Inert Mill Control System.⁴ Costs would vary if the entire process train was inerted, but this can be calculated based on the volume of the system and the number of air exchanges required. The operating costs and capital costs can be compared between an inert system and a pressure rated system in the selection of an appropriate strategy. Generally, the capital cost of an inert system is more cost effective than a pressure rated system. This can vary, depending on the equipment involved.

Some materials may actually generate oxygen during a process, which effectively renders inerting as not being economical or practical.

How to Inert?

Once the decision has been made to use inerting as the means via which to mill the explosible material, the next decision is what type of system is best suited to your process and budget. An inert mill can range from a very simple design to one with

more precise controls. The system cost rises proportionately with the complexity of the controls. The process engineer uses risk analysis to determine the system most appropriate for his/her process. Following is a brief description of some available systems.

Types of Systems

Simple System

An example of a simple inert mill is shown in Figure 1. In this example, a conical screen mill is simply configured with a small port in the infeed chute and a vent port either in the lower portion of the mill or further downstream. When the N_2 gas enters the mill, it naturally flows downward through the mill. The N_2 infeed stream is equipped with a pressure regulator, solenoid valve (activated by a timer), flow meter, and flow switch to ensure that there is a constant flow of N_2 into the mill. If the flow of N_2 falls below a particular pre-set point, the mill is stopped. The mill is purged with N_2 before and during periods of operation. Simple calculations are done to determine the purge time and flow required for displacing the O_2 in the mill, prior to start-up.

This represents the most economical and straightforward solution. However, there are no controls on the amount of O_2 in the mill.

Inert Mill with Oxygen Monitoring

Inert milling with oxygen monitoring is the most common option employed. It monitors the oxygen content in the air/inert gas mixture and controls the amount of N_2 introduced into the system.

Gas sampling occurs on a continuous basis. A Venturi/aspirator draws the gas from the mill through a set of filters. This filtered gas mixture then flows through an O_2 sensor, which sends a 4-20mA signal to the analyzer. The analyzer converts the signal into an oxygen concentration in %.

In this system, there are two set-points: a warning level and a target/alarm level. The target/alarm level is the Maximum Oxygen Content (MOC) and the warning level is usually set at about 2% below the target level - *Figure 2*. If the O_2 concentration increases above the "warning level," the N_2 flow is increased to bring the mix back to the desired percentage. If the O_2 concentration reaches the target/alarm level, an alarm will sound and the mill shuts down. N_2 will continue to be purged into the mill until an operator turns the purge off. If nitrogen is used as the inert gas, it should not be exhausted into the process room because it may cause the asphyxiation of operators. For some systems, a local exhaust system is used to accept the vented nitrogen and the exhaust from the sampling panel. For others, the exhaust is recycled back into the process train. Some customers may opt for the additional nitrogen monitoring feature in the process room, as an added safety precaution - *Figure 3*.

Various types of HEPA filters can be used, dependent on whether the powder being milled poses a "bio-hazard" threat. This is one of the many examples of "specific requirements."

Conclusion

In conclusion, inert milling is becoming more important in today's pharmaceutical processing facilities, given the large amount of powder being processed. Before choosing to inert, there are several points that need to be considered. To answer the question "why inert?" the product has to be properly characterized.

To determine "when to inert,?" the economics and design of various explosion prevention/protection strategies ought to be considered. And finally, to determine "how to inert,?" the process should first be determined in partnership with your mill supplier. Overall, inert milling is a popular choice due to the lower costs associated with it when compared to building pressure-resistant process trains. Proper testing and process design by reputable and experienced firms are recommended.

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This article presents the features and possibilities of a modern Multiple-Effect Water Still (MWS).

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Features and Possibilities of a Modern Multiple-Effect Water Still

by Mika Pärkkä, Juha Mattila, and Teppo Nurminen

Introduction

Over the last decades, distillation has maintained its position as the preferred method for the production of Water-for-Injection (WFI). The major reason for this is the simple nature of the evaporation phenomenon: impurities tend to remain within the liquid phase because of their associated intermolecular forces and bonds. When engineered efficiently, distillation processes are relatively simple where water will only evaporate at the required temperature and pressure. Distillation is intrinsically safe because when these conditions are not correct, the process will simply refuse to operate and distillate production will cease. With other water purification methods, critical process malfunctions are not as easily detected and can go unnoticed. Whenever pressure differences exist within the process equipment from the impure side to pure side, a potential contami-

nation hazard will inevitably exist. A typical modern Multiple-Effect Water Still (MWS) is presented in Figure 1.

Distillation processes have remained virtually unchanged for three decades. Only a couple of different still types are widely used, i.e., Multiple-Effect Water Stills (MWS) and Vapor Compression (VC) Stills. These are generally well known so emphasis will not be put on the basics here.

Because the basic principles have remained constant, the development efforts in WFI production equipment have focused on providing flexible products that best suit the required applications, facilities, and utilities. For example, distillate pumps are frequently no longer required, pure steam can be generated simultaneously with WFI, and the entire distillation unit can be sanitized automatically. These modern features assist in simplifying process validation requirements and also the daily operation.

Operating Costs

Consumption of utilities of a multiple-effect still varies depending on several factors. Adding more effects (columns) reduces the consumption of both plant steam and cooling water so that in normal operation a 7-effect MWS consumes little to no cooling water. Cooling water is needed regardless of the number of effects in a MWS, but this is also the case with a VC still because the compressor and its motor need cooling. Inlet temperature of feed water as well as outlet temperatures of distillate and effluents affect plant steam consumption in both still

Figure 1. A modern multiple-effect water still.



types and cooling water consumption in a MWS. Consumption of electricity depends only on the production rate in both. Depending on unit size and utilities, in practice a 6- or 7-effect modern MWS has similar operating costs to a VC still with similar capacity in hot operation. An example of calculations is presented in Table A. Consumptions were taken from manufacturers' brochures and the costs for utilities used were: plant steam \$6.00/1000 lbs; electricity \$0.11/kWh, and cooling water \$1.50/1000 gal.¹

Separation of Impurities

Distillation processes remove impurities since they remain in the liquid phase with pure water evaporating into the gaseous stage. Normally, the accumulated impurities in the water phase can then exit the system as one continuous output after all evaporation stages. In a new orientation of multiple-effect water stills, the reject outlets can be arranged in a more sophisticated way to improve the efficiency of the process. Since the impurity separation takes place independently at each stage of a multiple effect still, part of the impurities also can be rejected directly from each phase, without allowing them to travel unnecessarily through the entire system. This way the water that is not evaporated - and passing to the next stage - does not accumulate all the unwanted elements, and the impurity concentration does not increase considerably stage-by-stage. There are two benefits for this arrangement. First, the process heat transfer surfaces have less potential to accumulate elements that can cause scaling in the evaporator. Second, since the final reject from the last column will have a lower concentration of impurities, part of it can be recirculated back into the system improving the efficiency of the process.

Unlike other distillation processes, the MWS separation mechanism takes place in three stages, which adds to its reliability as a distillation method: evaporation, 180° turn, and centrifugal separation. Each purification phase has a dedicated function, which allows for greater control under varying conditions. Evaporation itself quite efficiently leaves

the unwanted elements into the liquid phase. The 180-degree turn in the lowest part of the column utilizes gravity to separate heavier elements - like water droplets - from the steam flow. This stage of purification is especially efficient when the process is running at a lower capacity, and consequently at lower steam velocities. The third stage - centrifugal separation - on the other hand works best for high steam velocities. These two complementing stages eliminate impurities and carry-over over the entire velocity/capacity range. This arrangement also enables the stage-by-stage rejection mentioned earlier and completely eliminates the need for demisters.

Non-Evaporated Feed Water Recirculation

Normally, a MWS operates with a blowdown rate between 10% and 15%. Generally, this is a suitable amount for removing impurities and producing good quality distillate even if the feed water quality is poor. Lower blowdown rates can be used with a higher quality feed water, but a certain amount of non-evaporated feed water should always be removed from the last effect in order to ensure smooth operation of the still.

Since highly pure feed water is expensive, it is valuable to recover as much as possible to reduce operating costs. A more recent development to achieve this objective is the recirculation of non-evaporated feed water from the last stage of MWS back to the feed water tank. This design leads to a reduction in the amount of blowdown and thus feed water consumption. Depending on the feed water quality, this will not compromise distillate quality because a significant amount of impurities are removed in the spiral sections of all the columns. The reject water from the first stages is not remixed with feed water, and it is always dumped to the drain. Blowdown rates as low as 3-5% can be achieved with this process. Cooling water consumption also can increase slightly because the feed water temperature increases, but savings are obtained since feed water is typically more expensive than cooling water.

Output	200 gph @ 97°C				200 gph @ 80°C			
	Consumption/hour		Cost/hour		Consumption/hour		Cost/hour	
	MWS 6 effect	VC	MWS 6 effect	VC	MWS 6 effect	VC	MWS 6 effect	VC
Plant Steam	390 lbs	300 lbs	\$2.34	\$1.80	390 lbs	220 lbs	\$2.34	\$1.32
Electricity	2.0 kW	11.2 kW	\$0.22	\$1.23	2.0 kW	11.2 kW	\$0.22	\$1.23
Cooling Water	16 gal	0 gal	\$0.02	\$0.00	65 gal	0 gal	\$0.10	\$0.00
Total			\$2.58	\$3.03			\$2.66	\$2.55
Output	1600 gph @ 97°C							
	Consumption/hour				Cost/hour			
	MWS 6 effect	MWS 7 effect	MWS 8 effect	VC	MWS 6 effect	MWS 7 effect	MWS 8 effect	VC
Plant Steam	3030 lbs	2620 lbs	2300 lbs	2040 lbs	\$18.18	\$15.75	\$13.80	\$12.24
Electricity	3.2 kW	3.2 kW	3.2 kW	68.0 kW	\$0.35	\$0.35	\$0.35	\$7.48
Cooling Water	154 gal	0 gal	0 gal	0 gal	\$0.23	\$0.00	\$0.00	\$0.00
Total					\$18.76	\$16.10	\$14.15	\$19.72

Table A. Consumptions and costs of utilities MWS/VC.

Max. capacity/ l/h		Footprint / m ²		Capacity / footprint / l/m ² h	
MWS	VC	MWS	VC	MWS	VC
979	1134	2.82	4.53	347	250
1739	1512	3.15	4.99	552	303
3477	3024	5.08	5.99	684	505
6365	6048	5.85	9.10	1088	664
10450	11340	9.93	16.35	1052	694
Max. capacity / gal/h		Footprint / ft ²		Capacity / footprint / gal/ft ² h	
MWS	VC	MWS	VC	MWS	VC
258	300	30.4	48.8	8.49	6.15
459	400	33.9	53.7	13.54	7.45
918	800	54.7	64.5	16.78	12.40
1681	1600	63.0	98.0	26.70	16.33
2760	3000	106.9	176.0	25.81	17.05

Table B. Footprints versus capacities MWS/VC.

Simultaneous Pure Steam Production and Distillation

For continuous pure steam demand, a separate Pure Steam Generator (PSG) is usually recommended; however, the pure steam production capabilities of MWS also have evolved in recent years. Traditionally, water stills have allowed some pure steam to be drawn from the process, but the available pure steam mass flows have been quite limited.

New process control strategies allow versatility for the process modes. For instance, the pure steam pressure can be maintained at the desired level not depending on the pure steam production rate. Pure steam production can take place during normal operation without interfering with the distillation process. The amounts of pure steam that can be produced during WFI production can, with recent designs, be up to 40% of the capacity of an equal size PSG. Occasional pure steam demands – like sterilization of tanks or pipe networks - can consequently be performed without a dedicated PSG. This way the footprint of the production equipment also remains considerably smaller than with separate, dedicated systems. Validation and maintenance costs savings also can be realized since one single unit is used.

Since pure steam is drawn directly from the WFI production process, it naturally fulfills all the WFI quality criteria when condensed.

Sanitization of Feed Water Lines

Most water stills have a sanitization sequence, which can be run when the unit is started up initially and after a period of downtime. These sequences usually only apply on the clean side of the still where the probability for bacterial growth is naturally lower. Normally, the feed water piping of the still can't be sanitized without special measures, which can pose a higher risk of contamination. It is expected that since the feed water is run through the still, microbial growth will be eliminated while potential contamination in the distillate is being led to drain during the sanitization phase. This think-

ing is basically correct, but there can always be a risk of contamination from feed water piping to either direction- the purified water loop feeding the still or the hot side of the still. The lower the operating temperature of the still, the greater is the risk of contamination.

Enhanced designs allow the flow to be directed from the condenser to the feed water line while the unit is run at a low plant steam pressure and cooling water supply remains closed. This way the cold piping including feed water break tank also can be routinely sanitized. A minimum temperature of 80°C for sanitization processes in the coldest spot of the piping can easily be reached using this method.

Distillation Against Back Pressure

WFI distribution piping should be kept as simple as possible. Each additional component in a WFI line introduces a potential hazard, both microbiologically and mechanically. This is especially true for pumps, compressors, or other pieces of equipment with moving parts. A distillate pump is a critical component, and whenever it can be avoided, a significant cost-saving can be reached.

Recent enhancements in multiple-effect distillation technology allow the distillate output to withstand the resistance induced by the back pressure in the distillate pipe. Distillate tanks are often fairly large and tall, and more often than not the distillate outlet of a Water Still is located lower than the WFI tank input. Traditionally, this issue has been circumvented either by adding a dedicated distillate pump or designing the environment such that distillate can always flow by gravity, which inevitably leads to increased unit height.

If the gas removal efforts in a Water Still are centralized into the first part of the process, the outlet section of the still can be sealed with no connection or contact to the environment. This design eliminates the need for vent filters, and also allows pressurization of the downstream side of the MWS. This way the natural pressure induced by the distillation process can be utilized as the driving force for "uphill

	Modern MWS	Traditional MWS	VC
Softened feed water	Possible	Possible	Possible
PCC	Yes, simplified design	Yes	Possible
Need for distillate pump	No	Not necessarily	Always
Simultaneous pure steam production	Yes	Yes, small output	No
Sanitization of feed water lines	Yes	No	No
Non-evaporated feed water recirculation	Yes	No	No
Three-stage separation of impurities	Yes	Yes	No

Table C. Summary of features of a modern MWS, traditional MWS and VC.

distillation.”

Today, virtually any height difference between the Water Still and a WFI tank can be handled without a distillate pump - as long as the two are located on the same floor - and thus the hazard for downstream particle emission is greatly reduced. This simple and efficient design also eases the installation and maintenance due to the reduction of mechanical pumping systems.

Controlled Capacity

When starting up a distillation unit, the produced distillate has to be rejected to drain until the distillate quality reaches an acceptable level. Some distillate also is rejected when the unit is stopped and the process must be cooled down in a safe manner. Since these steps consume time and energy, they should obviously be avoided as much as possible.

If the distillation capacity of a Water Still can be adjusted proportionally, WFI production can automatically adapt to the demand based on the distillate tank level. Unlike an ordinary on/off -type approach, a proportional capacity control function reduces the number of required start and stop sequences, thus leading to optimized energy consumption and minimized downtime. Less valve actuations also will mean longer service intervals.

Automatic Balancing

The operating parameters of a water still have to be verified periodically. These maintenance activities include adjusting the flow rates and consumptions to match the original design criteria. Usually this requires qualified service personnel making the adjustments, and can take a fairly long time.

With a proper automated balancing function, the system automatically measures the critical parameters and adjusts the process accordingly without the need of operator intervention. The new operating parameters also can be verified automatically after the auto-tune sequence. Even more production time will be saved if this function can be configured to start automatically after normal production hours.

Softened Feed Water

Most pharmaceutical stills are normally operated with DI or RO quality feed water supply. A water still also can operate using softened feed water with activated carbon in certain conditions. This has been successfully shown with vapor compression and multiple effect water stills, many of which have been validated at various facilities. With the decreased quality soft water presents, there are some further considerations. For example, it is important to keep the amount of chlorine-bearing compounds low in the feed water to avoid the potential of corrosion and carry-over. Also, the unit has to be cleaned more frequently.

If softened feed water is used, the blowdown rate is increased above the normal 10-15%, but it is typically smaller than the total water discharged in a typical RO and water still set-up. These benefits are further attractive by the savings that can be reached in capital and running costs. The additional cost of softened feed water accessories to a MWS is minimal compared to RO/DI investment and running costs.

Even with reduced capital savings, softened water should be carefully considered as the only pretreatment prior to a distillation unit. Municipal water quality can vary significantly, not only from area to area, but also seasonally. Softening will generally only reduce water hardness, but a variety of other water contaminants can be present and can affect the operation of the still over time regardless of distillation method. These include levels of chlorine, ammonia, and silicates. Chlorine and nitro-chloro compounds are widely used for water disinfection; in addition, a variety of compounds are formed as by-products of disinfection due to reaction of chlorine with ammonia (e.g., chloramines) and other nitrogen-containing compounds. Chlorine gas and chloride compound precipitation can be formed on evaporation of the water, which will be corrosive to metal surfaces. Ammonia is particularly challenging, where an equilibrium will exist between NH_3 gas and NH_4^+ in solution depending on the pH. Ammonia is very soluble in water, so even though it is very volatile it may not be completely removed through a distillation process.² NH_4^+ can be removed by activated carbon or a polishing softener while NH_3 cannot³, although by adjusting to an acidic pH the equilibrium can be shifted toward NH_4^+ .

Silica also is a common element in many feed water sources. This cannot be removed using a water softener with activated carbon. At levels between 100-120 ppm, silica will form a scale depending on pH.⁴ Silica levels of 25 ppm or higher have the potential to form scale with a 25% blowdown rate. At a 10% blowdown rate as little as 10 ppm can cause scale. Silica is most effectively removed using RO/DI systems and may be recommended where silica becomes a scale issue.

Physical Dimensions and Unit Weight

When a new facility is constructed, the size of the unit is not necessarily very critical because enough space for the unit can be allocated during the design phase. When existing equipment is replaced or new equipment is considered for existing facilities, smaller space requirements both in terms

of footprint and height of the unit is beneficial. For example, new MWS designs have very efficient evaporators so a newer still with a similar capacity requirement has a much smaller footprint and height than previous designs. When the footprint is related to unit capacity, a modern multiple-effect will be an efficient solution in comparison to other still designs, as can be seen in Table B.

A further important aspect is the actual installation or flexibility in moving the equipment into the desired area. Very often doorways and corridors are low and narrow, or the unit has to be placed on a higher floor, and thus only very compact units can be hauled into the location with minimal structural modification. Often the unit has to be installed in several pieces in order to fit. Obviously, it is an advantage in these cases if the unit can be freely divided into several pieces, i.e., there are several natural locations where the unit can be separated.

In addition to installation requirements, improvements in design also have allowed for improved service requirements. Dismantling and reassembling heavy machine parts induces a safety risk for maintenance personnel, and therefore it should be avoided or minimized. Since MWS are divided to several units, or columns, the arrangement allows each distillation unit to remain relatively compact in size. This allows for easy removal of the columns, and allows access to all components. Other benefits of newer multiple effect still designs include reduced unit weight, a reduced need to reinforce holding floors, and quiet operation. These considerations are important with an increasing emphasis on health and safety.

Discussion

Selecting suitable equipment for a facility depends on several factors. Costs are one factor, but there are a number of other factors to be considered such as physical dimensions and weight, suitable functions, and service issues to mention some. There is no "one solution suits all" approach, but a neutral evaluation of different options from all points of view helps the user in selecting the ideal distillation equipment - *Table C*.

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This article discusses a survey performed at an Italian pharmaceutical facility, which considers the thermal treatment of off-gas and liquid waste.

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Plant Reliability of an Off-Gas/Liquid Waste Incinerator

by M. Giovinazzi, G. Iaquaniello, and B. Manduca

Introduction

The shortage of landfill sites for hazardous waste and the difficulties of disposing of waste outside the boundaries of the pharmaceutical facility which generated that waste are enduring trends supported by environmental authorities. Combined with the more stringent environmental limits being placed on atmospheric emissions, these factors encourage the use of incineration plants, which present an alternative to previous methods of disposal, such as landfill disposal for liquid/solid wastes and water scrubbing for gaseous emissions. Incineration also may be considered as the most cost-effective long-term method of disposal of hazardous wastes.

This article discusses a survey performed at an Italian pharmaceutical facility, which considers the thermal treatment of off-gas and liquid waste. The survey used quantitative analysis techniques and focused on specific aspects of plant reliability. The quantitative analyses provided important information for the design of new units, used in environments characterized by high loads of particulates, alkaline melting salts, and halogenic acids.

The information obtained during the survey can contribute to:

- optimizing equipment lifecycle cost
- reducing maintenance expenditures
- improving both reliability and plant and equipment safety

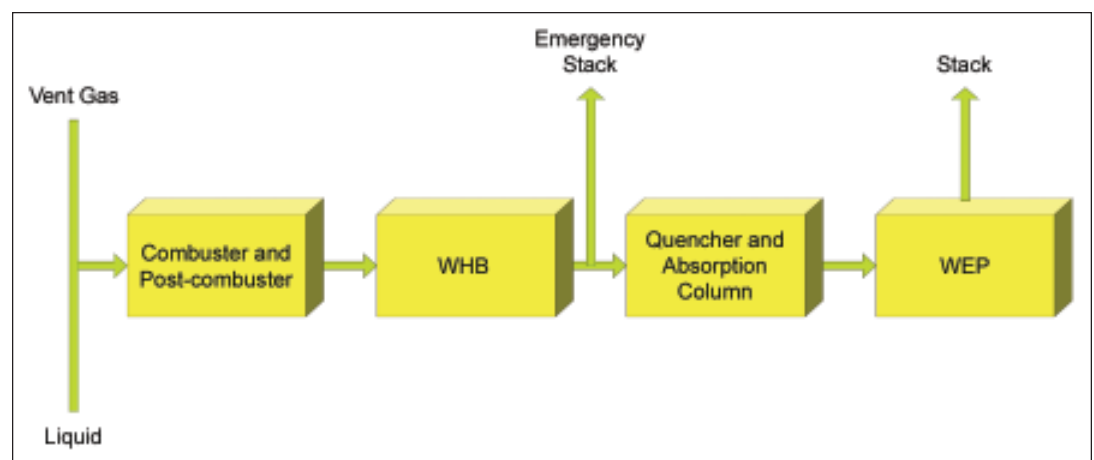
Reliability

There are several aspects to consider in determining whether equipment can be deemed as reliable:

- **Productiveness:** the overall amount of disposed waste over a fixed period of time
- **On-stream operability:** the percentage of time during which the plant is in operation
- **Demand availability:** the time during which the plant is operating at full capacity

The analysis of plant operating data demonstrated that demand was normally in the range

Figure 1. Process scheme of the off-gas/liquid thermal treatment plant.



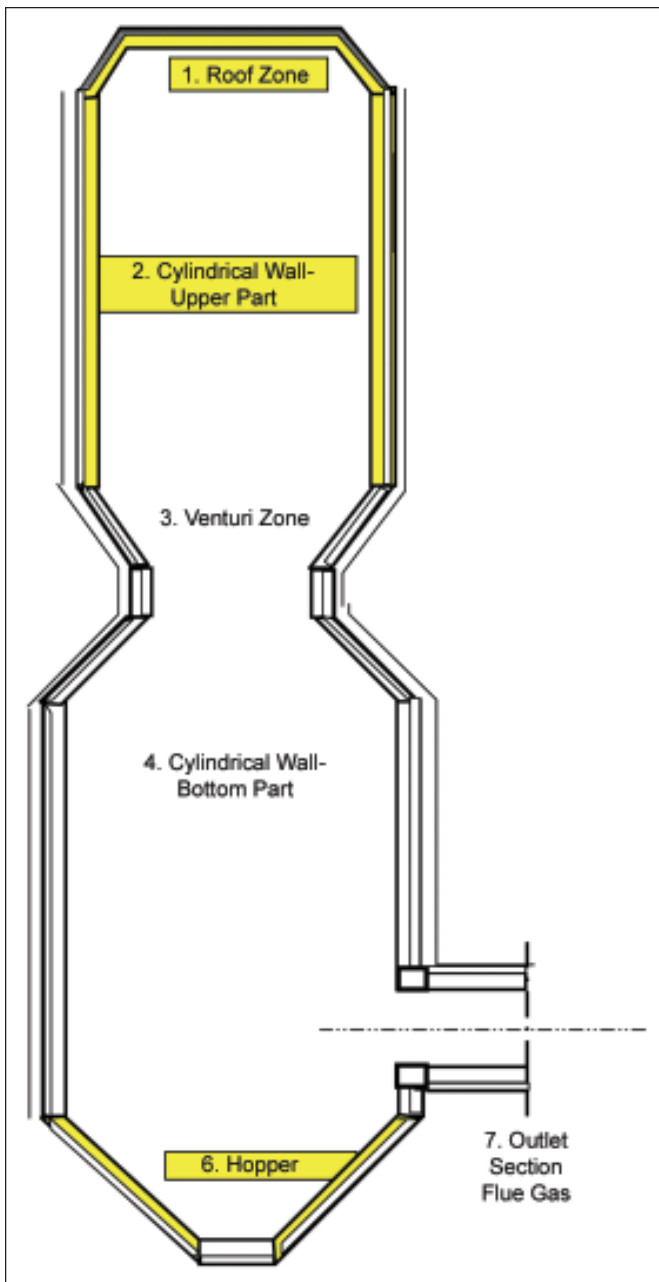


Figure 2. Combustor refractory lining.

of 80-85% of the nameplate capacity, which indicated that the main parameter requiring analysis was the time that the plant was 'on-stream.'

The plant reliability was affected by:

- the equipment and instrumentation redundancy philosophy adopted
- the design of equipment such as the combustion/post combustion chamber and the boiler, including the refractory lining materials
- the plant operation skills and the maintenance program

The ability of the unit operators to maintain plant reliability

depended extensively on:

- process scheme and design criteria adopted by the contractor
- waste storage philosophy
- feed stream handling
- level of technical support provided by the Maintenance Department

Liquid Waste Thermal Treatment

Figure 1 depicts the process block diagram for a typical liquid salts waste incinerator, which also has the ability to burn off-gases from production units. A vertical down fired refractory combustor precedes a water type boiler with two or more radiant sections and a mechanically cleaned convection section. The flue gas treatment consists of a venturi scrubber for particulate removal, an absorption column for removal of halogenic gases, followed by a Wet Electrostatic Precipitator (WEP) for aerosol and fine solid particulates, and a catalytic deNOx reactor for Nitrogen Oxides abatement (optional). An induced-draft fan is required to maintain a captive pressure in the combustor because of the important pressure drop across the system.

The capacity of the unit in terms of liquid waste disposal on an annual basis is 15,000 tons.

The complexity of such a scheme is indicated by its components; it is composed of 150 equipment items, 100 control loops, approximately 120 tons of piping, and 200 tons of structural steel. Piping materials range from carbon steel, to high alloy steel, to exotic plastic materials such as Polyvinylidene Fluoride (PVDF).

Liquid waste composition is reported in Table A, where a high content of low melting point salts, such as sodium chloride (NaCl) or sodium sulfate (Na₂SO₄) is clearly visible. These sodium salts (chlorides and sulfates) have melting points in the range of 760°C - 850°C although some eutectics may fall to 650°C -700°C, implying the presence of salt liquid droplets in the radiant sections of the Waste Heat Boiler (WHB). Downstream, such droplets can solidify into fine particulates.

As a result of the particulate load, silicon dioxide (SiO₂) and hydrogen chloride (HCl), which were produced by the off-gas, added to the already challenging environment, and produced a highly corrosive component, both at high flue gas temperatures and at low temperature (dew point).

Measurement of Reliability

One way to make a quantitative evaluation of equipment reliability is to look at unscheduled shut-down of the unit due to equipment failures, expressed in terms of lost days in the overall period of time considered.

In such an evaluation, equipment is considered to have failed when it is unable to perform its intended function. This

includes equipment failure/breakdown, both when the function is lost and if there is a reduction in functionality.

Table B shows all failure events and their causes over a period of three years. During this time, the unit was mainly disposing of liquid wastes, the off-gases being treated only in unusual, or emergency, situations. (The plant contained two incinerator lines; one dedicated to liquid disposal and the other to deal with off-gases, although off-gases could be fed automatically through both lines.)

The failure events were categorized into the following sub-classes:

- Rotating Machine
- Electrical/Instrument
- Mechanical
- Refractory Lining
- Plugging
- Other

Classification as 'Other' covered any occurrence that did not fit into the defined classes.

An average of eight failure events (causing unscheduled shut-down) per year were recorded with an average of two days lost per event. The most frequent failure event (causing scheduled shut-down) was a failure of the Refractory Lining in the vertical combustor. This resulted from continuous chemical attack and erosion by alkaline liquid salts and caused around 40% of days lost, but did not cause unscheduled shut-down. Such a result is, of course, based on a proper selection of refractory lining consistent with the presence of alkaline molten salts and halogenic acids, along with a well-prepared maintenance program.

Evaluation of Plant Reliability

Understanding plant reliability in quantitative terms provided useful strategic information. To calculate the plant reliability, in terms of availability 'on-stream,' the unscheduled shutdown period was deducted from the total plant operation time.

Table C shows the results presented as averages for the period analyzed for the on-stream evaluation.

On-stream availability was notably high, around 95%: achieved with a suitable design philosophy coupled to operator skills.

A dedicated maintenance program in such a harsh environment (high temperature, alkaline, coupled with molten salts and halogenic acid) is also fundamental in avoiding unscheduled shutdown. The importance of the scheduled shutdown for preventive maintenance and repairs is clear from the 5 week period per year dedicated to such work. The division of the scheduled shutdown into two separate periods was related to a number of local site constraints.

A. Liquid Waste Composition		% Weight (Range)
Water		60-80
Organic chlorinated solvents		5 -10
Organic solvents		5 -10
Salts		2 -10
B. Salts composition		% Weight
NH ₄ ⁺		5
Na ⁺		20
K ⁺		15
Cl ⁻		25
PO ₄ ³⁻		5
SO ₄ ⁻		30
C. Off-gas composition		
Nitrogen with chlorinated solvent and silane.		

Table A. Liquid waste composition.

Inspections were mainly by visual internal inspection of the equipment, which required access to the equipment. Repair work during shutdown was dominated by activities to replace or reinstall refractory linings in specific areas and to eliminate plugging, which occurred as a result of normal plant operation.

The overall plant availability of greater than 85% is also a good result and knowing this allows the site waste disposal schedule to be managed accordingly.

Major Failure Events

To gain a better understanding of the failures, the main failure events were listed in order of importance:

Start-up year	Nov 1999		
Period covered	3 years (2000-2002)		
No. events in the period analyzed (unscheduled)	24		
No. days lost in the period analyzed (unscheduled)	45		
No. Days lost in the period analyzed (total) (including scheduled shut-down)	150		
Note: the boiler was put into operation in 2001			
Specific causes for the above events and number of days lost per year:			
Events	Number of Days Lost		
	Total (Scheduled + Unscheduled)	Scheduled shut-down	Unscheduled shut-down
Rotating machine failure	2	0	2
Electrical/Instrument failure	10	5	5
Mechanical failure	5	3	2
Refractory lining	20	20	0
Plugging	10	5	5
Other	3	2	1

Table B. Failure events during the period analyzed (three years).

Unit	Days
A. as result of 8 failures	16
B. 5 weeks (in two different periods)	35
C. operating days	330
D. on-stream availability	95.2%
E. overall plant availability	86.3%
Legend:	
A. Number of days lost per year for unscheduled shut-down	
B. Number of days lost per year for scheduled shut-down	
C. Number of operating days: 365-B	
D. Percentage on-stream availability: $(1-A/C) \times 100$	
E. Percentage overall plant availability: $(1-(A+B/365)) \times 100$	

Table C. Plant on-stream evaluation.

1. erosion/attack/rupture of refractory bricks or cast material in the combustion/post combustion chambers
2. post combustion chamber ash discharge plugging, resulting from ash accumulation into the continuous ash removal system
3. thermocouples failure
4. vent gas burner nozzles plugging
5. failure of critical flow/pressure/level instruments
6. combustion detector failure

Plugging was the primary cause of unscheduled shutdown, and it also was responsible, either partially or totally, for some instrument/electrical and mechanical failures.

Qualification of Reliability Evaluation

The design approach and process knowledge together with engineering standards are important dimensions in determining reliability. It also is important to examine how the reliability evaluation is related to the specific maintenance program adopted in the plant, particularly:

- Real reliability depends on the level of redundancy of some critical elements of the plant. The redundancy level is only partially covered by codes and standards, and is related to the influence of local codes/rules, the client's standards, historical failure data, and capital budget.
- Frequency of element failure depends noticeably upon the owner's preventive maintenance program.
- Shut-down periods depend directly upon spare parts availability at the site warehouse/workshop.
- Major failure events also could be related to other site problems, out of the control of the plant (e.g., unavailability of utilities/electric power from the off-site main station).

To better analyze the reliability indexes of each plant, and to compare them, these features have to be clearly identified and stated separately to avoid misinterpretation of results.

A strong initial design for the waste handling strategy plays a key role in the optimization of future behavior of the plant:

- Correct evaluation of waste pre-treatment opportunities (stripping, liquid extraction, etc.) leads to a minimizing of the quantity of waste to be burned, and therefore, of the size of the plant, improving general reliability.
- Correct segregation philosophy allows a well-equalized waste mixture and maximizes the use of the plant, close to the design conditions. This, despite implying larger initial capital expenditures for storage tanks, allows running costs to be more cost-effective and increases the life of the plant elements.

The presence of molten salts and other solid particulates creates specific problems with the refractory lining and with plugging.

Refractory Lining Behavior

The two main concerns in the combustion and post combustion chambers are the refractory wear and replacement, and slagging of inorganic salts. Proper selection of the refractory lining based on chemical composition, physical properties, morphology, and bonding phases, together with cost, is critical to ensure an optimal lifecycle material cost. This consideration is important when the flue gas is aggressive, due to the presence of chlorinated and fluorine containing wastes.¹

Figure 2 shows the incinerator refractory lining. Two separate layers of bricks with different characteristics were installed. This is the most cost effective solution since the quality of the refractory lining heavily impacts its cost. Areas in yellow represent the zone where the refractory lining was replaced after three years of operation. This is normally a 250-hour job, if only the first layer is damaged, as occurred in the case described. This is the more common situation because of the direct exposure to process environment, particularly the:

- roof zone, where the burners are placed and liquid wastes are affected
- cylindrical wall-upper of the primary combustion chamber
- slag discharge at the bottom of the post-combustion chamber

Experience has shown that the use of very specific types of brick is the only way to cope with such an aggressive environment.

The most damaged area was the primary area chamber, in which the combined attack of molten salts and hard silica particles produced an erosion effect, reducing the thickness of

the brick to a point where replacement was required.

The damage to the roof zone chamber vault was related more to unusual/uncontrolled combustion conditions resulting in high temperatures in the vault itself. Solid depositions and plugging of the vent injection system, and/or waste liquid lances plugging, normally cause this problem. Attack on the outlet discharge nozzles was mainly due to the molten slag.

The sodium oxide produces a change of phase in the alumina, from α to β , the so-called alkali bursting in molten slag, which results in a change of refractory density and its successive breaking.

Some minor repairs were performed during the annual shut-downs. The overall behavior of the lining was quite good, considering the fact that the throat between the combustion chamber and the oxidation chamber, and the oxidation chamber itself had not been replaced.

Molten Ash Discharge Plugging Problem

The presence of molten salts coming from the waste liquid salts coupled with a large amount of silica from the decomposition of silane² created a very specific high particulate loading environment. Such a situation was worsened due to the reaction of sodium oxide (Na_2O) with silicon dioxide (SiO_2) to form a metasilicate. Na_2O may have been present from an excess of soda in the liquid wastes, or by decomposition of Na_2CO_3 or in Na_2SO_4 ($\text{Na}_2\text{O SO}_3$). Metasilicate is a sticky viscous glass at the combustion temperature of 1200°C , having a melting point around of 1050°C . It will solidify in any cold spot ($<1050^\circ\text{C}$). This was the primary reason for plugging of the ash discharging system.

To manage this, the discharge hopper was designed and arranged with a very specific geometry to avoid cold spots and allow a better run-off of the molten salts. Moreover, a burner was added on the connection between combustion chamber and ash discharging system to maintain the salts in a fluidized state.

After the removal of solidified salts from the bottom of the combustion chamber during the maintenance periods, it was often necessary to replace some parts of the refractory lining of this area, which were damaged both by the erosion of molten salts and by the removal process itself.

Conclusion

The reliability analysis presented leads to a better understanding of the nature and causes of existing and future equipment failure in a complex system, such as the highly salted liquid incinerator. Such knowledge can easily be incorporated into the design phase of the units, and also in the operator maintenance philosophy, through a dedicated inspection program and implementation of a master equipment database.

Local site characteristics and plant operational procedures are highly critical to reliability assessment.

Strategic decisions on the key points that affect reliability (redundancy philosophy, wastes segregation, mixtures equalization) should be discussed in the very early stages of design (conceptual design) in order to approach the matter in the

most cost effective way.

Preventive reliability assessment is increasingly advised to properly deal with local environmental authorities from the start of a project to help facilitate acquisition of required permissions.

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2005 Facility of the Year:

Novo Nordisk NovoSeven® Manufacturing Facility Employs Groundbreaking Modular Design

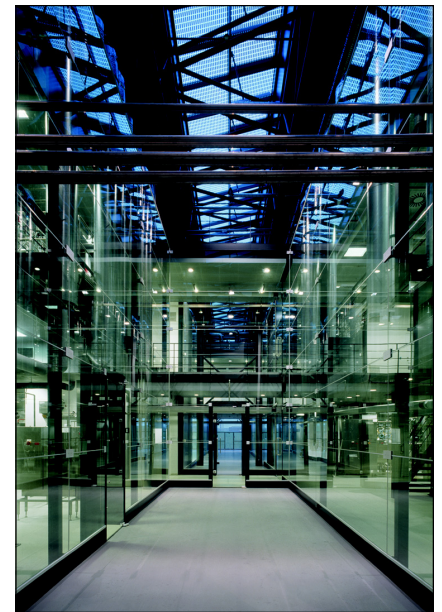
In 2000, Danish pharmaceutical company Novo Nordisk had an enviable problem: how to expand production as rapidly as possible in order to meet increased demand for its lifesaving NovoSeven® hemophilia drug. To build a new, dedicated NovoSeven manufacturing plant, Novo Nordisk set an aggressive delivery schedule that would have been impossible to meet, using conventional facility design/construction methods. Instead, the company embraced a revolutionary solution: modular design and engineering.

By going modular, Novo Nordisk was able to take delivery on the project after a fast-tracked 18 months – and the sleek new facility in Hillerød, Denmark is a powerful proof of the modular concept for the project's design, engineering and construction firm, NNE. The 14,000-square-meter plant is an integrated facility for mammalian cell fermentation, recovery, and

purification, with a large, open hall supporting independent production modules. The modular design will enable easy expansion as product demand increases into the future.

“The NovoSeven facility represents an industry milestone, by establishing modular engineering as an effective and powerful tool for rapid design and execution of pharmaceutical facilities,” said Kjeld Bjerregaard, NovoSeven Facility Manager. “The finished product is a thoughtfully organized building that demonstrates the result of modular thinking in the architectural design and construction, and in providing a safe and positive working experience for employees.”

This groundbreaking implementation of modular design and construction, and its use to accelerate construction and enable the company to respond rapidly to a pressing business need, has earned Novo Nordisk a cov-



The high tech appearance of the production area signals its critical function as the heart of NovoSeven® production.



The working environment is bright and open with many varied views to the outside from different places within the facility.

eted new distinction: 2005 Facility of the Year. The NovoSeven facility was chosen from an outstanding field of 28 global entries, each with powerful merits and award-winning attributes in its own right. Novo Nordisk was presented the Facility of the Year Award during the Plenary Session of the 2005 INTERPHEX exhibition, held in New York in April.

“The NovoSeven facility is an outstanding example of the high-quality, creative approaches pharmaceutical companies are taking to address key business challenges,” said Peter Bigelow, Chairman of the Facility of the Year Judging Panel. “Novo Nordisk deserves this recognition for several reasons: creative design within a super fast-track timeline for project execution, application of modular engineering for greater control and flex-

“The NovoSeven facility represents an industry milestone, by establishing modular engineering as an effective and powerful tool for rapid design and execution of pharmaceutical facilities.”

Kjeld Bjerregaard, NovoSeven Facility Manager

ibility, and dramatic and pleasing architectural features throughout the facility.”

A Modular Design/ Engineering Approach

From its initial stages, project design for the new NovoSeven® plant was driven by the requirement to reduce execution time as much as possible. “Even with everyone working as fast as possible, the schedule would not have been met through the traditional approach of executing major project components in series, by first constructing a building and then installing the equipment inside,” said Bjerregaard. Rather, the project team constructed process modules in parallel at offsite locations, where commissioning and qualification of each system could be conducted without the usual dependencies on adjacent upstream and downstream equipment.

Modules were divided into five subgroups: cell fermentation, chromato-

graphic separation, raw materials and buffers, clean utilities, and facility utilities. Each group of modules was purchased from a supplier with expertise in the specific type of equipment. The modules were ordered as complete functional and operational units, including instrumentation and power panels. A module for a purified water system, for instance, would be built and qualified to the requisite capacity on a skid, complete with instrumentation and control systems, and then be delivered to the site as a self-contained unit.

Meanwhile, the building was designed and constructed in independent sections, each planned to accom-



At this stage in construction, piping in the basement was already completed.

modate delivery and then meet the specific operating requirements of its respective process module. For the main production hall, mounting of equipment was particularly challenging due to the large number of modules and their close proximity on each other. The solution was to first construct the large hall and close the building for weather protection, and then afterwards to transport

all the process equipment into the hall and stage it in its proper place on the ground floor or first floor.

Distribution piping between modules (product, CIP/SIP, solvents and utilities, collection of waste, etc.) was a critical path issue for the modular design since it had to be installed and ready to connect as each module arrived onsite. Piping installation could not impede module delivery, and it needed to allow for adjustment in the event of



The third production area is open and ready for use if an expansion of the production capacity of NovoSeven® should be needed.



“The NovoSeven facility is an outstanding example of the high-quality, creative approaches pharmaceutical companies are taking to address key business challenges...”

Peter Bigelow, Chairman, Facility of the Year Judging Panel

unavoidable inaccuracies in the building design. To meet these needs, NNE installed the bulk of the distribution piping in the basement, which was completed and closed first to enable construction above ground.

Once modules arrived at the site, all that remained was to verify that off-site testing had not been invalidated in transit, to connect piping, power, and automation network cable, and to perform necessary on-site testing.

Facility as Art

Not only is the new Novo Seven manufacturing facility a living case study of modular design and engineering, but it's also an architectural gem. The beautiful structure was specifically designed to create an open, positive, and easily-navigated work environment, while remaining true to its core mission as a functional and expandable production facility. “Novo Nordisk used architecture and engineering to create a work of art – a building that is not only functional, but should bring great satisfaction to its employees,” said Facility of the Year Judge Ulrich Rudow.

The NovoSeven facility consists of four different components, each of which has a distinct structure and specific demands for surroundings, surfaces and HVAC. The four sections include the classified production area, a utility area for supporting processes and buildings, an energy center supplying power to the entire facility, and a common administration building with offices, laboratories, and employee canteen. “We wanted each area to ‘explain itself’ through the chosen materials and finishes. Glass and steel, for instance,



To create a feeling of unity and purpose among the employees, the offices and meeting rooms in the common building offer lots of views of the production area.

imply cutting-edge technology and smooth, sterile, and easy-to-clean surfaces – so they created an appropriate identity for the production area,” said NNE architect Charlotte Andersson.

While the four building sections were constructed independently and are designed as self-contained structures, glass corridors connect each section and provide cohesion among the different plant functions. Visiting inspectors often appreciate the corridors’ transparency, which provide them with a clear view of the production area. Furthermore, the clear layout of the corridors provides the staff with well-defined escape routes that are easy to navigate. Offices and meeting rooms in the administration building offer plenty of views of the production area, helping tie all employees

into the plant’s singular mission of producing NovoSeven®. “The goal is to make each person working in the facility feel part of a unified whole,” said Bjerregaard.

The glass and steel design of the large production hall and its supporting units is meant to visually connect the classified production area with the rest of the facility. The spacious walkways within the production hall played a valuable role during construction by facilitating the installation of modules and equipment. The production area’s high-tech appearance clearly signals its mission-critical function to staff and visitors, and its open and transparent construction helps employees gain a coherent picture of the whole facility and its many processes. At the same time, the transparent design supports requirements



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Ulrich Rudow, Facility of the Year Judge



The production facility at night.

for worker safety by enabling employees to overview a large area and detect danger signals early enough to take corrective action.

One Plant, One Product

At the time of Novo Nordisk's decision to build a new manufacturing plant for NovoSeven® in 2000, the drug was approved for treating hemophilia and other congenital bleeding disorders – but it was also being investigated in clinical trials to determine whether it could be used as a general hemostatic agent. This opened the door to a wide range of potential new applications and indications for NovoSeven® and made its real market potential difficult to pinpoint, as well as the timeframe that would be required for future clinical trials, regulatory approvals, and market penetration. As a result, Novo Nordisk had no clear projections of the future production capacity that would be required of the new facility.


Therefore, planning for the future had a two-fold objective: to expand production capacity as quickly as possible for the approved indication of NovoSeven®, and to build in the flexibility and expandability to accommodate future indications as they are approved. By offering this flexibility and enabling fast-track delivery of the plant in only 18 months, modular design and engineering provided the solution. “Flexibility is a key word when designing a production facility today,” said Klaus Illum, NNE's Engineering Director. “It is critical that the facility is able to change and adapt over time. New production capabilities must be integrated easily and cost-effectively as product and business requirements evolve.”

To accommodate future expansion, the NovoSeven facility's production area consists of three production units opening onto the main hall. At the time of handover, two units were operational; the third is a construction

shell that can be built out to accommodate future surges in NovoSeven® production. Looking even further ahead, the facility's repeatable design will simplify construction of a reflected duplicate of the entire plant, should product demand require it. In designing a facility that could accommodate the range of possibilities for future demand and indications of a single product, Novo Nordisk and NNE fulfilled their vision of “One Plant – One Product.”

Proving the Modular Concept

Handover of the NovoSeven facility in November of 2002 may have marked the completion of a successful project for Novo Nordisk, but it signaled an exciting new beginning for NNE. As the starting point and proof of concept for the design/engineering firm's modular engineering principles, the new facility provided invaluable knowledge to help NNE continue refining its principles and working methods. More significantly, the project gave NNE the impetus to continue working toward its strategic goal of building a greenfield pharmaceutical facility (from start of detailed design to start of performance qualification) in only 12 months. In fact, the experience gained from the NovoSeven® project enabled NNE to complete a subsequent facility in 14½ months.

“By delivering a facility in 18 rather than the standard 30 months, we took a huge step toward our goal of a 12-month facility,” said Illum. “But, just as important, the NovoSeven facility was a groundbreaking project that helped demonstrate the feasibility of modular design, not only for fast-track delivery, but for the inherent flexibility that modularity provides.” 



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