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Pharmaceutical Supply Chain Challenges

by Arthur St. Onge and Sean O. O'Neill

This article discusses the development of distribution networks above and beyond those currently in existence, and an exceptionally high level of coordination between the efforts of the pharmaceutical industry and the United States Government since the events of September 11th.

The pharmaceutical industry, from a supply chain perspective, faces two significant challenges.

The first is increasing pressure to reduce costs relating to the deployment and delivery of pharmaceuticals to the dispensing professional and ultimately to the consumer. This downward cost pressure, which cuts across all supply chains, has helped to drive the demand for even greater efficiency in the supply chain and will become yet more intense in the immediate future as companies struggle to improve their profit pictures. Supply chain managers have responded by implementing "best practices" processes, advanced logistics execution software, and to an increasing degree, automated material handling technology.

The second challenge remained unrecognized in a meaningful way prior to September 11th of last year. Almost overnight, America's vulnerability to bio-terrorism attack became evident as a still unknown source began sending anthrax spores through the mail with the intention of infecting its recipients. The creation of a Homeland Security Initiative has put into motion a series of programs that require significant pharmaceutical resources, including a new supply chain. Some of these programs are in the early planning stages and will become clear later in this article. This article addresses the dual challenges to the pharmaceutical supply chain: cost-cutting pressure and creation of a new supply chain to contend with bio-terrorism.

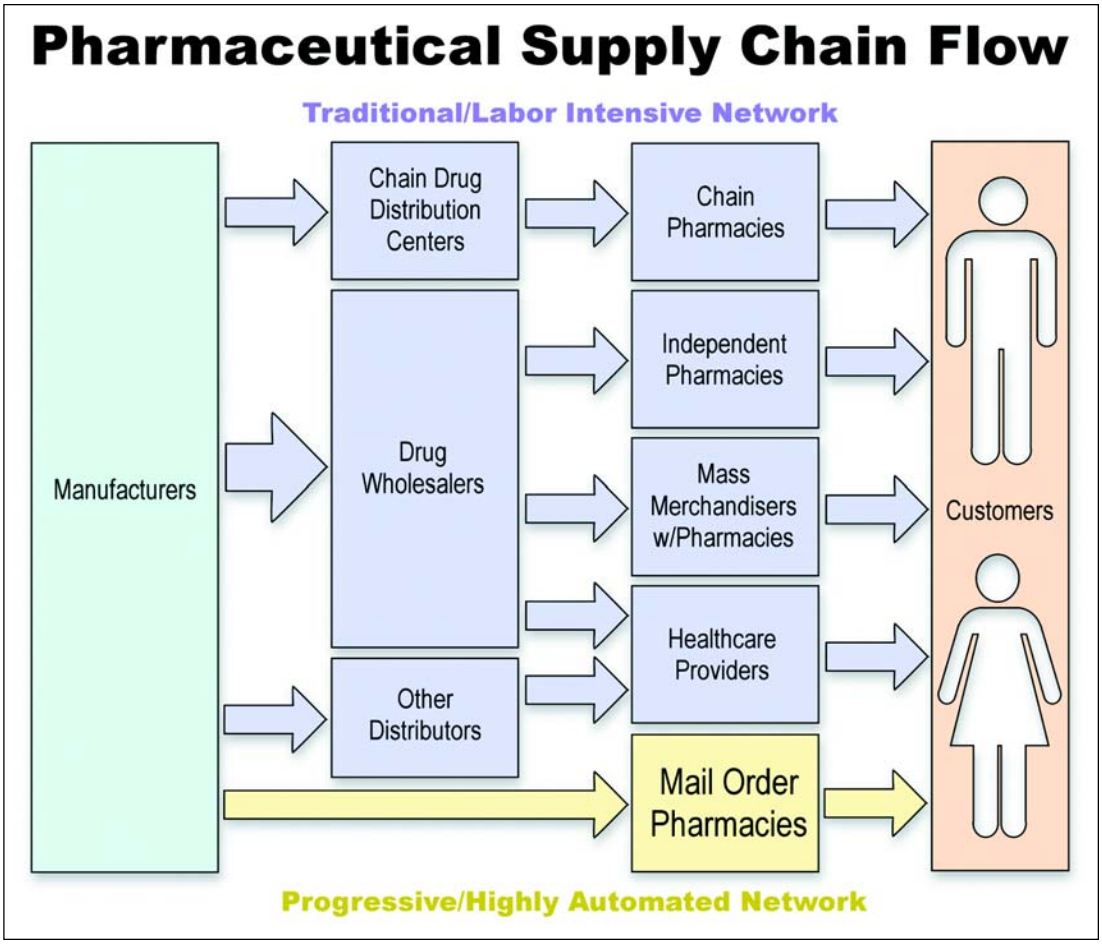

Figure 1. Pharmaceutical supply chain flow.

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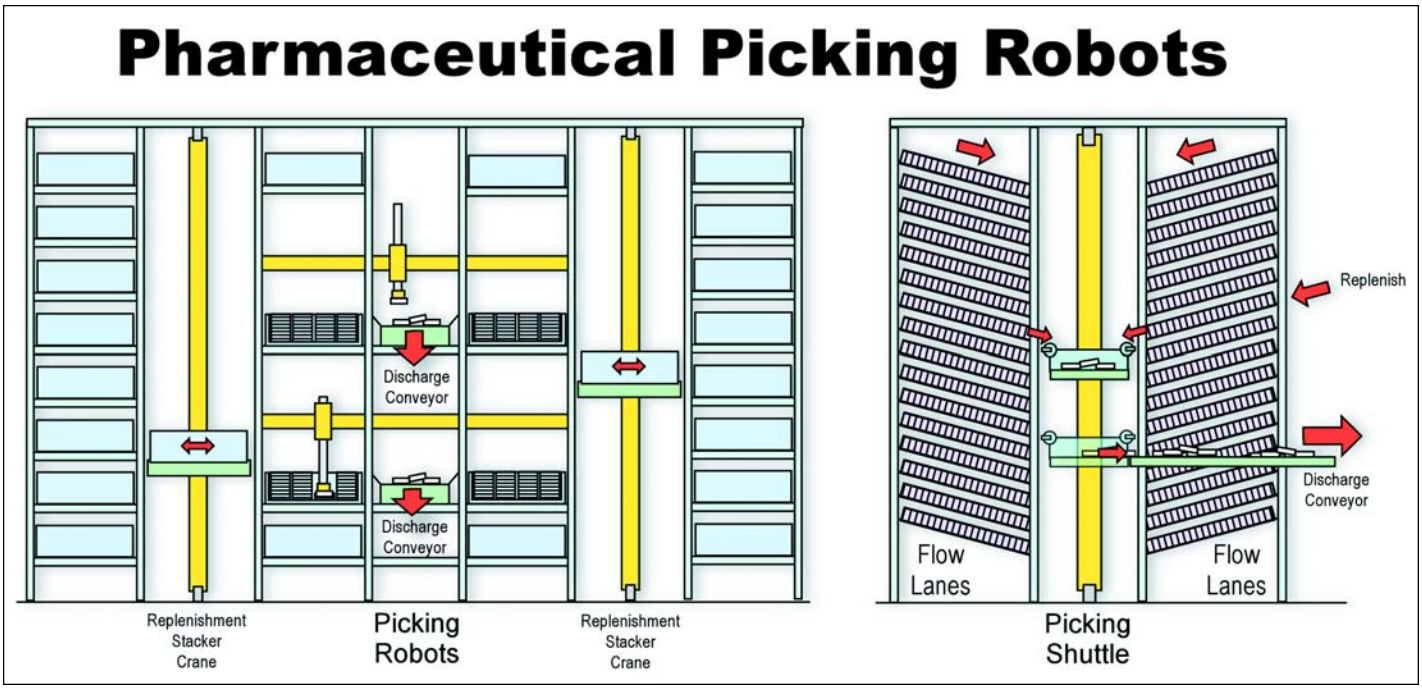

Figure 2. Pharmaceutical picking robots.

As depicted in Figure 1, pharmaceutical products originating at manufacturing facilities flow into a complex distribution network. Initially, about 88% of the product flow moves into the wholesale and retail networks. From these two primary distribution providers, pharmaceuticals flow downstream through various pharmacy channels where prescriptions are filled in face-to-face contact with the consumer (patient). Note that a growing number of patients, 65 million in the case of Merck-Medco, do not experience face to face interaction with a pharmacist since they are serviced though the burgeoning direct-to-customer mail order channel.

Cost-cutting pressure on the supply chain has resulted in several manifestations. For instance, from a strategic business perspective, there has been considerable consolidation in the wholesale pharmaceutical channel, including most recently the merger of Bergen Brunswick with Americsource. Consolidations seek to reduce cost in the supply chain by reducing redundant administrative and supervisory staff, and by strategically reinventing the distribution network, including the closing of redundant distribution facilities. The consolidation efforts aspire to achieve a network that retains the best resources of the pre-consolidation networks, thereby placing the company in a financially healthy position to service its consumers.

At the tactical level, supply chain managers focus on "best practices" processes, as well as technology to boost productivity. Wholesalers' distribution networks will often comprise 30 or more distribution centers. Even small productivity increases at a single distribution center, if implemented across the entire network, can produce significant savings. "Best practices" processes frequently focus on reducing waste or unnecessary tasks associated with a range of activities from the receiving of pharmaceuticals at a distribution center to the filling of customer orders. Using "lean thinking" principles, supply chain managers focus on areas of activity such as order fulfillment, a function that typically accounts for about 60% of all distribution center labor.

"Best practices" and processes in this function, depending upon overall throughput, includes analysis of various product slotting methods to arrive at the one which will produce the greatest order selection productivity. The goal when slotting is to reduce the distances walked by order selectors to a minimum, as walk time is non-productive. A first pass at slotting will analyze products in the pick line according to velocity; fast movers will be positioned toward the front of the pick area and positioned so as to be most accessible to the order selector. However, a more thorough analysis of customer order patterns may reveal that certain fast movers are frequently ordered with specific slow movers. This process is known as *clustering*, as analysis will lead to product being positioned in clusters of items most frequently ordered together. This type of process analysis and implementation requires software support.

The Logistics Execution System (LES) community, formerly known as Warehouse Management Systems (WMS) and Transportation Management Systems (TMS), offers software products that allow process changes to occur with little hassle. Referred to as re-configurable software, the LES vendor offerings enable the distribution center manager to easily adapt a new process and configure the LES to support it. Moreover, these software products support the analysis process as well, thereby helping to identify the applicability of a range of industry "best practices" to a given set of circumstances.

Additional advances in software are coming to market to further improve distribution center performance. Known as *resource planning and optimization tools*, these products allow a distribution center manager to develop a finite plan, one or more times daily, that considers all personnel and equipment resources and order demand. The resulting plan identifies the specific sequence of order release that will balance resources, optimize their utilization, and complete all work required for each item. These software products, which focus on optimizing distribution center performance, hold the promise of 10 to 15% improvements in productivity without changes to process or equipment.

The material handling technology industry continues to improve its offerings. For instance, material handling vendors such as SI Handling, Knapp, and PEEM have for years focused

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considerable attention on the pharmaceutical supply chain. Machines referred to as "A-frames" have helped to increase productivity and throughput capacity in many wholesaler and retailer distribution centers. A-frames dispense solid dosage products to fill customer orders, thereby eliminating the need for manual order selectors in this function. However, the machines require manual replenishment. Furthermore, the typical cost of these machines limits their application to high-velocity product. This leaves the low-velocity product to be handled manually and somehow merged with the high velocity product.

Recent developments in this technology sector include automated replenishment and robotic applications that encompass high- and low-velocity product handling - *Figure 2*. While only a few examples of these advances currently exist, primarily in the mail order channel, supply chain managers can look to these developments for productivity and quality improvements. As an additional benefit, automation reduces the nagging need to set staff levels in accordance with peak demand periods, either through a permanent or a temporary workforce. If properly sized, automation can handle variations in demand with a constant, manageable workforce.

Mail Order Pharmacies

Perhaps the most significant advances in technology productivity applications center on the mail order channel. Because of the extraordinarily high costs associated with the handling of product (dispensing tablets and capsules) by professional pharmacists, pharmaceutical companies have invested heavily in automation technology. Merck-Medco, the leader in this industry with 65 million patients, has established what could be characterized as fully automated pharmacies. In these centers, the observer witnesses a showcase of advanced material handling technologies designed to virtually eliminate manual handling in prescription preparations. Dispensing, packaging, literature preparation and insertion, mail pouch containerization, and sortation to some 700 zip code destinations occur without human intervention. The results are truly spectacular, allowing Merck-Medco to set the standard for low cost and high quality -- better than 6-Sigma.

While Merck-Medco is reluctant to share details about their state-of-the-art packaging and distribution facilities, their groundbreaking advances will eventually find their way into the wholesale and retail channels, thereby further enhancing supply chain efficiency.

Bio-Terrorism

As late as the middle of 2001, those aspects of the pharmaceutical supply chain devoted to outbreaks of disease perpetuated by terrorists would have scarcely registered on the supply

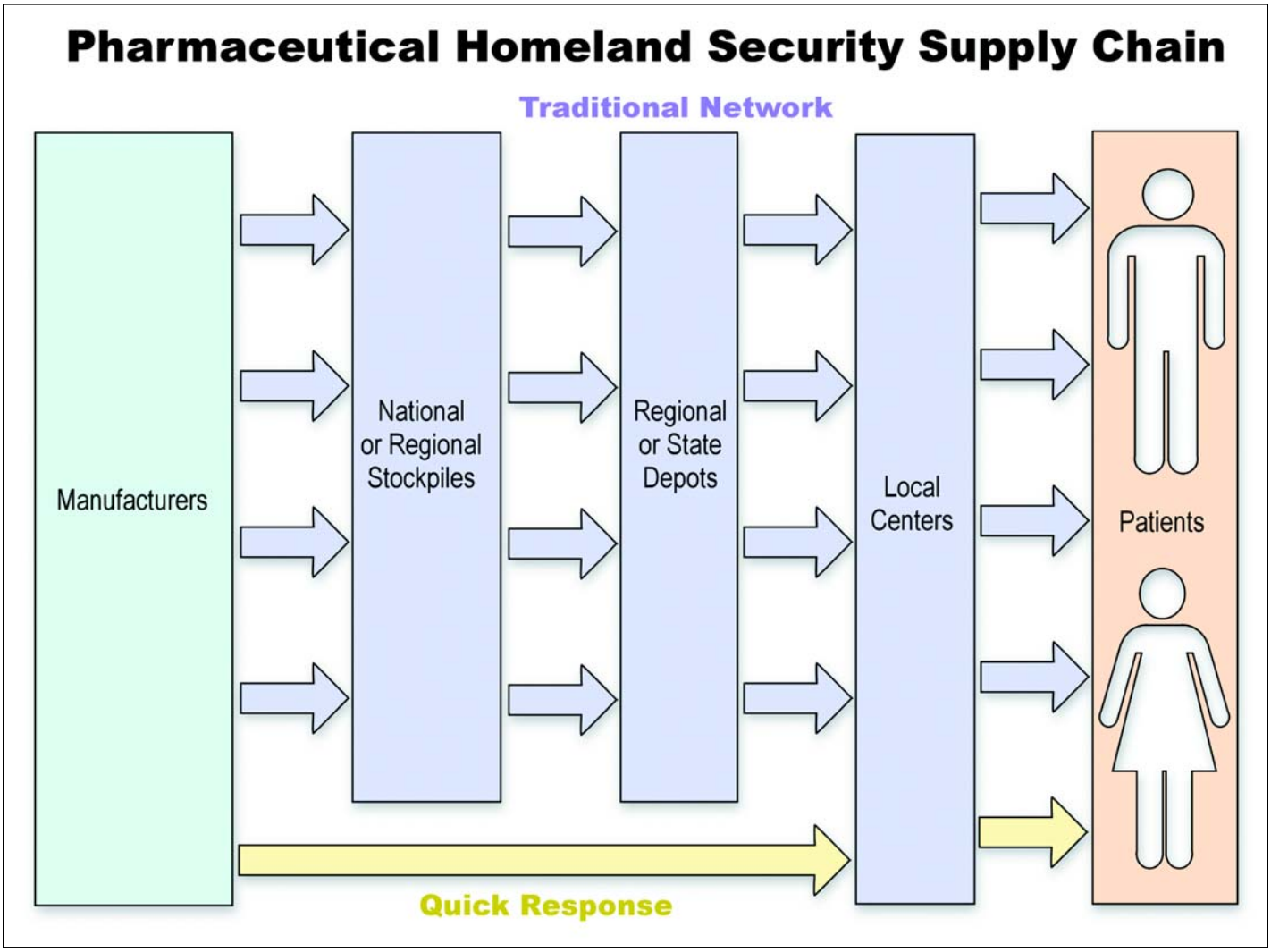

Figure 3. Pharmaceutical homeland security supply chain.

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> ***...automation reduces the nagging need to set staff levels in accordance with peak demand periods, either through a permanent or a temporary workforce. If properly sized, automation can handle variations in demand with a constant, manageable workforce.***

chain flow chart.

September 11th has changed that significantly. Now, under the Homeland Security Initiative, the pharmaceutical industry, government and private sector supply chain providers are working diligently in a concerted effort to prepare for potential threats. Missions of this emerging channel, which we'll refer to as the Pharmaceutical Homeland Security Supply Chain, include identifying potential bio and chemical agents that could be used by terrorists and preparing sufficient quantities of vaccines to protect citizens in large and vulnerable metropolitan areas from outbreaks of disease such as small pox or the plague.

The challenges are enormous. What bio agents pose a significant threat? Small pox, Q fever, Venezuelan Equine Encephalitis (VEE)? What is the antidote - a small pox vaccine, or a drug to treat unprotected victims? How much vaccine is needed (per dose and in total), how large is the potential threat, and where is it likely to appear? As if these challenges were not enough, there is also the issue of how to package products such as vaccines in single dosage units with proper literature for dispensing by Homeland Security-designated personnel.

Downstream supply chain questions must be answered in the planning stage. For instance, where should antidotes (vaccines, etc.) be deployed? In secure areas away from mainstream pharmaceutical distribution? Terrorists could attack vaccine supplies simultaneously with a major bio-assault on metropolitan populations.

Pre-deployed stockpiles of vaccines could be regionally or locally deployed to ensure the rapid treatment of victims. This entails risks. Control of these agents is critical in that they are the basis for the bacteria and could therefore pose a threat in the wrong hands. The alternative would be to manufacture and store centralized stockpiles of vaccines in several regional locations under a high level of control.

To fulfill the national demand, the CDC and pharmaceutical companies will need to pool their resources, both in terms of product development and manufacturing capacity. This process is currently underway. The major pharmaceutical companies have joined a Task Force on Emergency Preparedness. This task force has been formed to leverage the pharmaceutical industry, including research, development, and manufacturing capabilities in helping the government and our nation in the fight against bio-terrorism.

As we evaluate the Pharmaceutical Homeland Security Supply Chain in the context of stockpiled vaccines (Figure 3), it becomes apparent that its true effectiveness will be defined by the last link, administering the vaccine to the victim. Helicopters and airplanes can be deployed to move product to regional "hot spots." Ultimately, we may witness the local off-duty nurse administering vaccines at the neighborhood church. True efficiency must be achieved in this final step. Sterilized pre-kitted vaccine packages, similar to pre-kitted packages found in hospital emergency rooms, will be critical to the supply chain's success. This may well require new facilities where custom-packaging operations can occur.

In the case of an unanticipated bio-terrorism threat, the Pharmaceutical Homeland Security Supply Chain would be challenged in a different way. Isolating and identifying the threat and the associated cure/vaccine will become the critical first step. The second step will be the challenge of producing the needed vaccine(s) and deploying it to the victims.

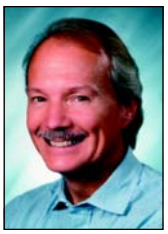
Pharmaceutical manufacturing capacity will be of critical importance in ensuring an effective response to the threat. The CDC and the Task Force on Emergency Preparedness should work together to create an *Emergency Response Manufacturing Capacity Database*. Facilities should be identified by capacity, product types, production flexibility, and production capability. Known threats should be matrixed against this database to identify viable candidate plants for producing the current and future vaccines required.

In the event of an incident, the validation of these facilities with these known vaccines will challenge the current FDA validation process. Fast track approval programs from the US FDA should be further challenged to identify new tools and procedures to increase levels of responsiveness. This type of effort, if properly studied, could become a mechanism for accelerating the current commercial process.

In summary, the pharmaceutical supply chain is in a state of flux. Traditional channels are experiencing consolidation and increasingly supply chain managers focus on process and material handling techniques for ways to increase productivity and capacity in response to continuous pressure to reduce drug delivery costs. The mail order channel where the cost pressures is greatest has led in applying advance systems applications, and the wholesale and retail channels will eventually benefit from these advancements.

The nascent Pharmaceutical Homeland Security Supply Chain poses issues regarding where, how, and under what conditions should vaccines etc. be deployed to thwart bio-terrorism. The pharmaceutical industry together with a host of government agencies are early in the planning and execution process of what eventually will be a robust supply chain.

About the Authors



Arthur St. Onge is President of St. Onge Company, a leading global consulting engineering firm. He is a frequent speaker at logistics, manufacturing, and distribution conferences and writes a monthly column for Modern Materials Handling Magazine. He began his career in 1963 when he joined his father's consulting engineering firm whose practice focused on refrigerated facilities. By the end of the 1960s, St. Onge's involvement with automated warehouse designs led the firm into the field of advanced material handling systems. In 1983, St. Onge and three associates founded St. Onge Company. In 2001, St. Onge Company launched Institute St. Onge, the logistics industry's first online knowledge management portal for logistics, material-handling technologies, and in-depth application in logistics, manufacturing, distribution, and train-

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ing. In 2001, St. Onge also announced the development of a distribution center scheduling software product that is known as Order Analysis and Planning Systems (OAPS), which is the first industry software aimed at optimizing distribution center performance. The firm holds several patents and has been instrumental in bringing new technologies and operations practices to many industries. St. Onge is the President of the Material Handling Foundation, and is a member of the Board of Governors, Material Handling Industry of America, Council of Logistics Management, Warehouse Education and Research Council, Global Supply Chain Forum, and the Institute of Industrial Engineers.

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This article evaluates the decision to replace sterile stopper preparation equipment with ready to use, sterilized stoppers.

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Ready to Use Stoppers: A Novel Outsourcing Alternative

by Douglas Stockdale and Robert S. Nase

Introduction

During an assignment to develop additional sterile preparation operation capacity for a pharmaceutical client, a new outsourcing service being developed by West Pharmaceutical Services was evaluated. The service being developed was the delivery of stoppers rinsed in hot USP Purified Water and further rinsed in Water-For-Injection and terminally sterilized, ready for use in sterile manufacturing.

The pharmaceutical client had built a drug manufacturing facility and current demand for the product necessitated multiple capacity expansions. A bottleneck or constraint was developing in the sterile preparations department of the Formulation and Finishing suite. Earlier facility expansions had locked the Formulation and Finishing suite into the middle of the facility and resolving the constraint became a very difficult task.

One of the alternatives was to replace the sterile stopper preparation equipment with ready to use, sterilized stoppers. The facility space which would be gained by the demolition of the stopper preparation equipment would then be available for other essential sterile-preparation operations that could not be outsourced.

The decision to outsource the sterile stopper preparation was further complicated with the pending installation of an isolator filling line. The ready to use stoppers needed to be provided in a manner that was acceptable for both a traditional cleanroom aseptic filling line and the new isolator aseptic filling line.

Figure 1. Westar RS stoppers final rinsed with Water-For-Injection are packaged under controlled cleanroom conditions prior to sterilization. (Photo courtesy of West Pharmaceutical Services.)

Outsourcing Decision: Why Outsource?

There are a number of reasons to outsource. An obvious reason is to improve the time to market. Second, a dedicated supplier team may be more effective than an internal project team. A third reason to outsource is to gain access to alternative resources through available capacity, manpower, resource expertise, or leverage financial resources (i.e., capital spending). The decision to outsource should only be made after you evaluate your core competencies and available resources (financial and human) around the project requirements.

For the client company, the preparation and sterilization of stoppers was not considered a core competency; however, a successful record of aseptic product processing with few defects was. Thus, the decision to outsource a critical sterile process was a complicated decision made by company management. Outsourcing also was considered by the client company to leverage the capacity and manufacturing experience of another supplier by utilizing a service that was within the core competency of the supplier.

Outsourcing Decisions: Critical to the Future Success of the Organization

The decision to outsource was based on a series of financial assumptions that had to be validated. Some of the investments were in the expense category, i.e. change documenta-

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tion, personnel time to complete the evaluation and implement the changes. Some of the investments were capital, i.e. specialized equipment to implement the changes. For the stopper outsourcing decision, most of the investments were in the expense category. Anticipated expenses, either direct or indirect, included the Engineering, Manufacturing, and Quality Assurance personnel time required for qualification and process validation testing. There would eventually be an opportunity to utilize the excess facility capacity created by the outsourcing, but the capital and expense incurred would be associated with the new process equipment. Nevertheless, a decision to implement the sterile stopper supply also was a decision to allocate the critical personnel resources of the facility.

The company's competitive position could be placed at risk with the decision to outsource without a close working relationship with the stopper supplier. If the supplier is unable to provide the service in the time required, the quantity and quality required, then the current operation could be impacted. The effect of the impact could vary from a temporary delay in production to a product recall. Therefore, a very thorough evaluation was required of the supplier for capacity, financial soundness, reliability track record, and quality systems.

If the supplier is unable to perform, then there is a potential for a long-term negative impact on business. Equally, a long-term relationship was being created by the removal of process equipment, eliminating that capability internally, and relying fully on the resources of the supplier. Thus, a final evaluation was made that if the relationship did fail, what is the contingency plan? Can the process change be reversed to provide a needed safety net for the decision to avoid an uninterrupted supply of stoppers?

The regulatory impact also needed to be considered in the decision to outsource the preparation and sterilization of stoppers. What would be required to complete regulatory approval of the manufacturing change? This assessment needed to be made with the Regulatory Affairs, Quality Assurance, and Validation functions of both organizations, and with the assistance of the FDA. After the Regulatory plan was determined, the remaining implementation program could be developed. An important part of any decision was the development of a project plan that provided a high probability for a successful implementation within the time frame required.

Core Decision Making Processes

To recap the decision making process, the project objectives must be clarified: provide manufacturing capacity. The next step was to perform a business assessment and determine the amount of risk. A financial analysis was then completed. Next, an outsourcing partner assessment needed to be completed and then to develop a joint implementation project plan.

Benefits of Ready to Use Stoppers: A Novel Alternative

Ready to sterilize stoppers and components that are washed and rinsed in hot USP Purified Water and further rinsed in Water-For-Injection are final packed into a low particulate, low bioburden bag that is designed for direct entry into sterilization units - *Figure 1*. The packaged components are then delivered to the end user for terminal sterilization.

A process is being developed that would further add value to these ready to sterilize stoppers by adding a sterilization step after the packaging process. The final package configuration must be compatible with the sterilization process to be used and also be capable of facilitating placement of the components into the aseptic filling process. One method being considered by the company for this application is shown in Figure 2. This method allows for a completely closed system, capable of being steam sterilized after filling of the components. The port end is designed to mate to a Rapid Transfer Port system allowing a totally aseptic transfer into the isolator or aseptic filling system.

Since components will be used directly from ready to use packaging, the quality attributes associated with the delivery of these components to the filling line (i.e., lubricity) and maintenance of the ultimate drug product integrity (i.e., stopper dryness in the case of lyophilization and some powder filled product) must be considered. Partnering with the component supplier in the development stage will assure quality attributes and processing requirements are realized both in the process and on the final filled product. In order to develop and agree to specifications for certain quality attributes, samples of stoppers in the company's existing stopper preparation operation were evaluated for dryness and silicone or lubricity quality. Likewise, the stoppers obtained from the supplier's process were evaluated until the process was established to yield comparable quality attributes to the process being replaced.

The key to a good supplier relationship is establishing a cross-functional project team with representation of all necessary departments from both companies. In this case, both companies had equal representation from Engineering, Quality Assurance, Regulatory, Validation, and Operations. West also supported the project with Technical Customer Service representatives to provide the necessary technical input and Sales representation to assure a smooth transition when placing engineering, validation, and production orders. Technical Customer Service further provided coordination between the companies' test facilities to assure sound interpretation of test methods and results. Routine meetings between the companies have allowed for open communication and free exchange of data as well as issue resolution by utilizing project management and problem solving techniques.

Establishing a thorough understanding of both companies' process and product flow is another key milestone in developing the outsourcing program. Bottlenecks or constraints within each organization are readily identified when utilizing process mapping techniques. A detailed and well-constructed process map also can be used to identify areas within the respective manufacturing operations that could eventually result in a process or product failure. The process map also will assist when utilizing quality and engineering techniques such as Failure Mode Effects Analysis (FMEA) to model the "To Be" process and identify potential areas of failure before the process is fully established.

Prior to implementation of the validation process, both companies must agree on the Validation Master Plan (VMP).

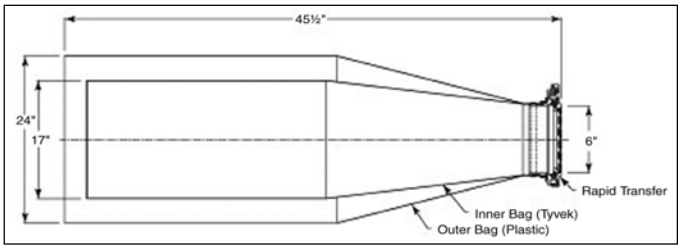

Figure 2. SteamPac is a packaging option that transports Westar processed stoppers into a barrier isolator system. (Photo courtesy of West Pharmaceutical Services.)

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In the case of the supplier, the establishment of the VMP was critical to timing the delivery of ready to use, sterile product to the drug company. Since taking a critical operation such as sterilization out of the direct control of the drug company, it was important that the "sterile" standards used by the company were well communicated. The VMP was reviewed and critiqued by the drug company to assure all critical aspects of the sterile validation were incorporated and a clear understanding of change control requirements was established in order to maintain the system upon successful completion of the validation.

Conclusion

Both the company and West Pharmaceutical Services continue to pursue the smooth transition of ready to use closures. As this development project moves forward, the cross-functional project team maintains an active project management schedule including routine meetings, information and data exchange, and constant updating of project schedules and issue resolution.

About the Authors

Douglas Stockdale is the President and Chief Executive Officer of Stockdale Associates, Inc., a management and technology consulting company for the life sciences industry. He has more than 25 years of practical operational experience, which includes 20 years with Baxter Healthcare prior to founding Stockdale Associates. He is a very active speaker, writer, and advisor to the industry. Stockdale has a MBA from University of La Verne and BS in package engineering from Michigan State University. He is a member of ISPE and PDA and has one patent for a medical device. He is on the Educational Advisory Boards for University California, Irvine (UCI)-Extension Medical Device Product Development Certificate, the University of California, Los Angeles (UCLA)-Extension Biomedical Short Course program, and the Education Committee for ISPE's Greater Los Angeles Area Chapter.He recently developed and is a lecturer for the UCLA Extension Biotechnology Short program series. The series includes Quality Systems, Process Validation, Aseptic Filling, and Container and Closure Development for Biotechnology.

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This article focuses on the components and the equipment for secondary packaging. It has been adapted from a presentation conducted at a two-day seminar entitled "Packaging Parenterals" in Philadelphia, PA, June 2001.

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Design for Success: Secondary Packaging and Labeling

by Nancy St. Laurent

Introduction

This article aims to act as a guide to ensure all necessary efforts are expended for a successful pharmaceutical package and advocates that Team Effort is critical to the success in the development of packaging solutions. Pharmaceutical packaging is divided into two categories: primary packaging and secondary packaging.

Primary Packaging

Primary packaging may be defined either as the packaging material used to form a primary container, and directly contacts the drug product, or as the method of placing the drug product into its primary container.

Secondary Packaging

Secondary packaging is defined either as any packaging subsequent to product placement in the primary container or the components of such packaging, such as the labeling, cartoning, or case packing.

Secondary packaging is the final area of manufacturing before the product is shipped to the customer. This article focuses on the components and the equipment for secondary packaging.

In order to determine whether the development of a packaging solution has been successful, criteria should be defined against which to measure the level of that success. Such criteria include:

- Low Cost Packaging Materials
- Low Equipment Costs
- Low Cost of Goods Sold (CGS)
- Low Rejects
- High Quality Product Protection
- High Productivity
- High Yields/High Throughput

Packaging Development

Where secondary packaging comprises only simple packages, such as labeling a container and placing it into a shipping carton, little effort is likely to be required in development. For new, unique dosage forms, or custom packages; however, considerable effort should be spent on developing the secondary package. Packaging development requires input from a multitude of departments within an organization, and each department must be given the opportunity to provide input in their area of expertise:

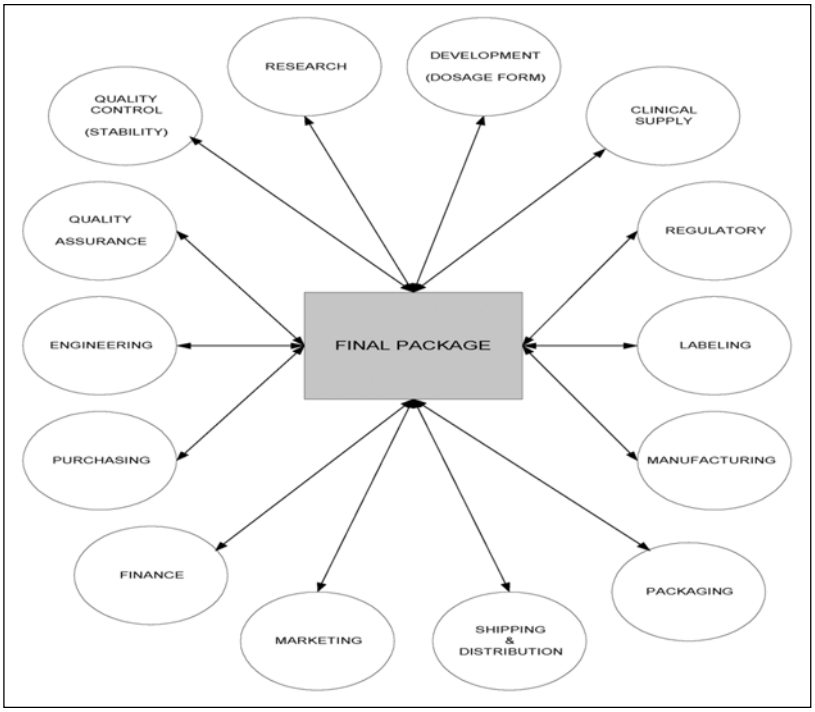

Figure 1. Organizational team functions.

Members representing all necessary organizational functions (Figure 1) should be formed into a team early in the process of developing and designing a packaging solution. The entire 'team' should be involved in the complete development process, from the preliminary stages of the package design through to development of the final package.

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This article discusses the benefits of such a team approach and provides an overview of the individual departmental responsibilities involved in packaging design.

Package Design

In the early stages of package development, it is important to maintain a flexible approach to the final design, because a preferred package may be later found to be either too costly to produce or not feasible to manufacture from an engineering standpoint. Developing both preferred and alternative packages, and ensuring that packages can be produced at a low cost, improve the likelihood of success of a packaging design.

Initially, it may be beneficial to develop only the concepts of the package, particularly if it is a new custom package, or where the package design does not incorporate standard packaging materials. Cases where such an approach may be beneficial include:

- Carton style: printed or corrugated - different machinery is required to handle each carton style. (For example, while in the process of purchasing bulk-cartoning equipment, a medical device company kept changing the carton from a simple RSC corrugated design to a complex chipboard printed carton with numerous folds, etc. Bulk-cartoning equipment could not be selected until the final carton style had been decided.)

- 50-count tray: a package concept was developed; however, before the final package was determined, many variations were evaluated until the least costly, most producible package was selected. These decisions ranged from purchasing a thermoformed tray and lid to forming the packaging on the packaging line.

- Hospital packs: constantly changing delivery systems mean that packages must be updated to keep up with the latest methods.

- Syringes: many controlled dose syringes were packaged five syringes to a pack. Hospital storage system changes resulted in a need for a package reconfiguration.

- Inhalation, drug delivery devices: many new dosage forms are being developed and unique packages will be required. These will be custom designed packages, requiring custom equipment.

Departmental Involvement and Responsibilities

Each department representing an organizational function has specific responsibilities in the packaging development process, which follows the progression both of the development of the packaging and of the product.

Research and Development (R&D)

R&D develops the dosage form so that it is stable, safe, and efficacious. The packaging requirements will depend on the dosage form of the product, which may be:

- Tablet, Soft Gel, Capsule
- Liquid
- Oral
- Parenteral
- Solid/Powder
- Parenteral - Liquid or Lyophilized
- Topical Cream/Ointment/Patch

Depending upon the characteristics of the product, there will also be product protection criteria, such as temperature, light, or percentage Nitrogen cover, all of which need to be determined by the R&D Department. These requirements definitively determine the primary package, but also can affect the secondary requirements as well.

Clinical Materials and Supply

Clinical Materials and Supply adopts R&D's criteria in producing and distributing clinical trial material. As clinical trials progress, adjustments may be necessary to the packaging criteria, based on stability, shipping, etc. Results of such distribution issues should be transmitted to the team involved with the development of the final package.

Quality Control/Quality Assurance (QC/QA)

It is critical that QC is involved with all testing requirements of the product in its designated package, and assists in developing stability testing and product testing. Such tests may impact the packaging operation, e.g., expiration dating as it affects labeling. Both QC and QA monitor product storage temperatures, e.g., filled products stored in refrigerated conditions that need to be at room temperature prior to labeling. Such factors may affect the packaging line requirements, such as speed or packaging batch size.

The number of packages to be tested is determined by both QC and QA, but QC samples for laboratory testing, while Quality Assurance samples for product and package quality characteristics. QA also is responsible for monitoring packaging line set-up, label placement, cap torque, product quantity, etc.

QC has specific responsibilities for packaging material and performs a critical role in qualifying packaging material suppliers. QC sets up tests for materials, receives them, tests and releases them to packaging, and monitors each batch of packaging materials to ensure quality. QC may need to acquire new testing equipment and this needs to be considered in costing the packaging. A comparator may be required where there are critical package dimensions. Some syringe packaging has very critical packaging components. Where critical defects are discovered, it is important that either QC or QA has the appropriate testing equipment. Vacuum testing equipment may be necessary where products are placed in vacuum-sealed packages.

QA must be involved in equipment selection and determining the validation protocol. QA assists in performing validation on the equipment, in developing Standard Operating Procedures (SOPs) for equipment operation, and packaging operations. It also may assist in developing operator-training programs on new processes.

Regulatory and Labeling Departments

Labeling should be developed to meet requirements of regulatory agencies, such as the FDA, EPA, and EU. The potential effects of proposed new insert regulations should be kept in mind. The Regulatory and Labeling Departments are responsible for determining how the labeling is incorporated into the package; the information that is required on the primary package, i.e., the vial or the bottle, and that required on the secondary packaging, i.e., the carton or the shipping case. If the

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primary package is stored unlabeled, the container may need pre-identification. If the primary container is labeled; however, inspection may be required prior to labeling. QA and QC usually are involved in determining the level and type of inspection. Inspection can be done after labeling and at various other stages of the packaging operation.

Information to be preprinted on labels, or cartons, etc. and which information will be printed on-line need to be determined. Several languages may need to be included and patient information may be required. Bar Code requirements depend on the type of product, whether it is a prescription, over the counter drug, or a medical device. Bar code information may be determined by the product manufacture. In many cases, there is no regulatory requirement. The type of printing used, such as laser, thermal transfer, ultra-violet or ink; may affect label design. For example, at a plant that introduced laser printing to cope with the number of labels that required printing, all labels required the addition of a color block where the laser print was to be applied.

The type of printing used and the type of label used must be determined prior to equipment selection. Various options include:

- Pressure Sensitive
- Thermo Sensitive, Thermoplastic
- Shrink Labels
- Mylar Labels
- Sleeve

Alternative printing/labeling methods, such as on-line printing of labels, cartons, and inserts also should be considered. On-line printing is popular in Europe, but is not widely used in the US.

Distribution tracking may be required. If this is the case, then bar coding may be preferred. The Regulatory Department needs to be prepared for changes to labeling just prior to regulatory approval. This may happen several times just prior to the introduction of a new product to the market. Once a drug is on the market and adverse side effects are found to occur, these will necessitate changes to the labeling.

Labeling may need to accommodate ERP or MRP systems. For example, an MRPII system installed at one location required the purchase of new ink jet coders for all printing requirements. The MRPII system automatically assigned nine digit lot numbers, whereas manually determined lot numbers, used prior to the installation of the MRPII system, were only three digits in length.

Purchasing

Purchasing must ensure that only qualified materials are purchased (for the best price) and should have access to alternate qualified vendors to ensure uninterrupted supply. Materials also must be purchased in a timely manner to prevent delays to material supply.

Corporate initiatives on packaging materials must be carefully examined to ensure that they have no adverse effect on the product and package. One such initiative was the standardization of parenteral rubber stoppers, worldwide. Had this change occurred, there would have been a dramatic impact on product stability studies and stoppering equipment in locations around the globe.

Packaging, Engineering, and Purchasing must work closely to send out complete Requests for Quotation (RFQ) for equipment. Purchasing can assist in qualifying vendors and once selected, has the responsibility to finalize any agreements, such as pricing, delivery, and warranties. Purchasing also may assist with expediting delivery.

Engineering

Engineering considers pre-selection of equipment and works within the team to specify equipment that will produce a package at the lowest cost. This department assists in preparing RFQs to be sent to qualified vendors. Engineering prepares documents, such as building line layouts and utility requirements.

Once vendors and equipment are selected, Engineering needs to participate in engineering reviews. As a minimum, Engineering, Packaging, and Quality Assurance need to participate in the preparation of the Validation Protocol. This group also works with vendors on Factory Acceptance Testing and documentation packages, etc.

Once equipment is received, Engineering needs to assist in:

- Installation
- Start-up and Commissioning
- Installation Qualification (IQ)
- Operational Qualification (OQ)

Engineering also provides both maintenance and training on equipment operations.

Finance

Finance prepares/approves justification for equipment purchases. This department prepares cost analyses of the product, package, and equipment and needs to ensure adequate CGS and payback analysis, etc.

It is crucial that Packaging, Engineering, and Purchasing are involved in decisions with Marketing to determine elements such as the packaging, the labeling, and the distribution requirements. Marketing assists with sales forecasting which has a critical impact on equipment requirements.

Marketing can be the critical focal point to a successful package and must remain open to approval of alternatives in cases where the preferred package is either too costly or not producible, as was the case for the 50-vial package mentioned earlier in this article. Marketing conducted focus groups prior to the package change. Storage, labeling, disposal requirements were all critical factors recognized by the focus groups. Again, there is a significant difference in packaging materials in Europe, which is focused on the more biodegradable 'green' packaging, versus the US, which uses more plastics.

Manufacturing

Manufacturing has a critical impact on the success of a package and needs to ensure that product quality requirements are met, such as product sterility, tablet hardness and moisture, and the consistency of creams and ointments.

The transfer of product needs to be controlled and Manufacturing needs to integrate with Packaging in all aspects, such as:

- Form/Fill/Seal Operations
- Parenteral Operations
- Continuous Operations for Powders, Tablets
- Flow of Materials from Manufacturing to Packaging
- Storage of Product between Manufacturing and Packaging

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> ***Labeling should be developed to meet requirements of regulatory agencies, such as the FDA, EPA, and EU.***

Packaging

Packaging needs to understand all the requirements for the package in order to see that all equipment is specified, ordered and integrated. This includes all major requirements, such as Form/Fill/Seal (F/F/S), labeling, cartoning equipment, and minor packaging requirements, such as printing and case sealing. Packaging recommends whether existing equipment can be used or new equipment needs to be purchased. In the latter case, Packaging needs to be involved with the rest of the team to ensure that the most productive equipment is purchased. Packaging is responsible for evaluating the primary, secondary, and any tertiary packaging requirements, including the preferred controls and whether the existing available space will suffice, or further space will need to be allocated.

If custom equipment is required, Packaging has an interest in determining the cost impact of the equipment on the final package.

Where integration between vendors is needed, this may be performed either in-house or by using external sources, in which case Packaging and Engineering need to select a qualified external integrator.

Packaging should participate early in the development process to consider factors that determine whether the package is "producible." Such factors include:

- potential requirement for modification of the package design
- sales forecasts
- batch sizes
- storage requirements
- safety factors, such as ergonomic considerations. Where high volumes are anticipated, automated equipment is needed to avoid work related incidents, such as carpal tunnel syndrome, etc.

Packaging needs to determine a development timeline, the culmination of which is dictated by the date on which product is required for sale. This timeline needs to account for the requirements for Factory Acceptance Testing of the equipment, the completion of the facility in preparation for receipt of equipment, and the time required for start-up, commissioning, and validation.

What inspection is required for the package or the product and the quality of inspection, e.g., Optical Character Verification (OCV), and Optical Character Recognition (OCR), fall under the remit of the Packaging department, in conjunction with QA, which establishes the inspection criteria.

Packaging has to consider the logistics of labeling, including the preferred type of printing, e.g. laser, the type, whether on-line printing is used, and the supplies required, e.g., inks. The Packaging Department and QA are responsible for determining what inspection is required for labeling.

Packaging also is responsible for considering personnel issues, such as ergonomic considerations, e.g., weights of materials, product supplied, skill levels, and training requirements. It is critical also to consider availability of labor in the area and the labor skills required They must comply with OSHA requirements for lifting, MSDS requirements, i.e., solvent exhaust, personnel protection, etc.

Shipping and Distribution

Shipping and Distribution is responsible for meeting product storage requirements, how the product is to be shipped, and whether the product requires refrigeration or freezing. Additional controlled space, such as coolers or freezers, may be required.

The number of packages, which may be case lots or individual packages, are considered by Shipping and Distribution, in relation to the ultimate destinations of the product, which may include:

- Hospitals
- Distribution Centers
- Pharmacies

Products may require repacking in the shipping area or they may not. Certain products may also require additional product protection during shipping. Temperature monitors may be required for critical products.

Summary

Just one missing link can significantly affect the success of a package design. Many product or package launches fail because of the lack of consideration of **all** of the factors discussed in this article. The failures range from a package that does not hold up in the field, purchase of inefficient equipment, selection of sub-standard materials, or excessive rejects due to faulty package design.

It is therefore, critical to adopt a team approach and allow each member of that team to contribute fully to the entire design process.

About the Author

Nancy L. St. Laurent, CPP, is the Chief Operating Officer of CRB LINCS, a division of CRB Builders. LINCS, Line Integration and Consulting Services, is targeted to be a major integrated provider of fill and finish equipment lines, including consultation, design, procurement, installation, and start-up. Previously, she was president of St. Laurent Packaging, Inc., a manufacturer's rep firm for filling and packaging equipment. She has spent 35 years in the pharmaceutical industry, starting with Wyeth in Pennsylvania. She was in manufacturing management with Wyeth and then with Fort Dodge and SmithKline Beecham Animal Health facilities. She was director of production at Fort Dodge and held management positions in both pharmaceutical and secondary biological operations at SBAH. St. Laurent was a charter member of the ISPE Midwest Chapter and is past president of the Chapter. She is past chairman of the ISPE Membership Services Committee. St. Laurent has been a speaker at ISPE events and is currently a Director in the Society as well as co-leading the Packaging and Warehousing Baseline® Guide Task Team.

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Total Cost Assessment methodology provides a standardized approach to identifying costs and benefits associated with environmental, health, and safety issues for industrial products and processes.

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Merging Environmental, Health, and Safety Costs into a Decision-Making Model

by Joseph E.L. Rogers

Business decisions today are based on rigorous financial analysis using the rules of a company's basic accounting system. Accounting systems and related supporting information packages vary in the level of complexity they can support for business decisions. They typically focus on easily identifiable costs, such as capital, labor, materials, and allocated indirect costs. Many businesses now realize that there are other factors -- such as potential Environmental, Health, and Safety (EHS) costs, employee satisfaction, and community relations which can and should be included in the decision-making process. These costs, while real, are less tangible and sometimes hidden. Documenting and quantifying these costs so that they can be included within the typical financial decision-making methodology and defended to top management creates a significant challenge.

Through the work of the American Institute of Chemical Engineers' CWRT,[1] Dow Chemical has made progress in addressing this challenge of combining tangible and intangible costs, as Samuel L. Smolik, Vice President for Global EHS recently indicated.[2] "Historically, projects were discussed in either the language of economic value or of environmental performance, but we've figured out how to translate from one language to the other." The process being employed by Dow is a customized version of the Total Cost Assessment (TCA) methodology developed and validated by an industry collaboration assembled by the Center for Waste Reduction Technologies (CWRT).

TCA is a multi-disciplinary, scenario-based decision tool that complements traditional economic evaluation models by examining all costs and their timing associated with a decision, including contingent and future intangible EHS costs. The methodology is designed to allow users to include Life Cycle Assessment (LCA) information in the decision-making process, if it is available, but it can be used successfully without this information.

To ensure widespread usefulness, the CWRT task force included representatives from ten multinational companies in the chemical, pulp and paper, pharmaceutical, and other consumer products industries (Table A), resulting in a methodology that is broadly applicable to many industrial sectors, including semiconductors and telecommunications.

The first phase of the project, completed in 1997, was a survey to determine the specific needs for an industry-validated tool for TCA. In response to these needs, the task force developed a multi-disciplinary, scenario-based costing methodology[4] that complements traditional cost models by facilitating an examination of all costs associated with a decision. When applying the TCA methodology, the decision team considers hidden costs, such as monitoring costs, potential fines, remediation, and property damage. The methodology also provides for and encourages the inclusion of intangible costs, such as the effects of changes on worker morale, community relations, and brand value. Finally, the method allows decision makers to consider the totality of internal, company-borne costs side-by-side with an estimate of costs borne by society, such as the potential effects of greenhouse gas emissions and habitat degradation. Information on this final category of "external costs" is provided in part by the method's ability to integrate environmental LCA results with

Table A. Total Cost Assessment Task Force Members.

Bristol-Myers Squibb	Merck
The Dow Chemical Company	Monsanto Company
Eastman Chemical	Owens Corning
Eastman Kodak	Rohm and Haas Company
Georgia Pacific	GlaxoSmithKline[3]

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Cost Type	Description
I: Direct	Capital, labor, materials, waste disposal
II: Indirect	Non-allocated corporate and plant costs (e.g. reporting costs, regulatory costs, monitoring costs)
III: Future and Contingent Liability	Potential fines, penalties and future liabilities (e.g. non-compliance, remediation, personal injury, property damage, industrial accident costs)
IV: Intangible - Internal	Costs borne by the company (e.g. customer acceptance, worker morale, union relations, community relations)
V: External	Costs borne by society (e.g. effect of operations on housing costs, degradation of habitat)

Table B. Environmental, Health, and Safety Cost Types in TCA Model.

the internal financial analysis. LCAs quantify the total economy-wide pollution and resource consequences of product or process life cycles, estimating the cumulative effects of the supply chain as well as usage and end-of-life disposition.

TCA is a decision-making tool, intended for stand-alone use, to evaluate different alternatives. It is not designed to replace an organization's traditional accounting system, but rather to provide cost or benefit (cost avoidance) information for internal managerial decisions. Each company will have its own policies, principles, and values that will guide how the TCA model is applied within the company.

Environmental, Health, and Safety Cost Types

Traditional accounting methods used for decision-making typically focused on direct costs (capital, labor, materials, and waste disposal) as well as indirect costs (reporting costs, regulatory costs, and monitoring costs). The TCA model goes further by defining three additional cost types, as shown in Table B. Direct (Type I) and indirect (Type II) costs are easy to measure with standardized accounting methods already in place. Contingent liability, intangible, and external (Type III, IV and V) costs are more difficult to measure, so the task force developed methods to estimate their effects.

For example, one method to quantify Type V costs is to employ contingent valuation. To measure Type V costs associated with pollutant discharges to surface water, contingent valuation applies a willingness-to-pay methodology for predicting natural resource damages. This method assumes that individuals' behavioral responses to reductions in resource services can be simulated in a survey questionnaire. In other words, values for resources can be estimated by soliciting individuals' expressed preferences for them. The assumption is that expressed preferences are consistent with the behavior individuals would reveal in a market if it existed.[5] Contingent valuation criteria ask the basic question: how much is the reduction in utility for an injury to a natural resource worth to an individual?

The contingent valuation method of cost estimation does, however, have its shortcomings. Respondents' reported willingness to pay may be greater than their actual willingness to pay. Since the questions are hypothetical in nature and respondents may have pre-existing biases, the results obtained may be inconsistent.[6] Inaccuracies inherent in the contingent valuation method can be reduced by applying additional cost estimation methods. Costs associated with pollutant discharges to surface water also can be estimated by the cost of market transfers for purposes of environmental protection. For example, state and federal agencies periodically purchase or lease water to augment flows on major rivers to minimize impacts due to hydroelectric power generation or agricultural demands. The purchase price, in dollars per acre-foot, can then be used as another estimate of the value of the surface water body. Combining the two valuation methods, contingent valuation and market transfers, a distribution of potential costs incurred due to damaging an equivalent surface water body can be obtained.

By defining costs in this way, TCA permits the user to handle variables that do not directly impact the manufacturing process.

The Seven Steps of TCA

TCA methodology consists of six main steps and a final feedback step that provides input into a company's decision process. A series of real-world applications of the method to date

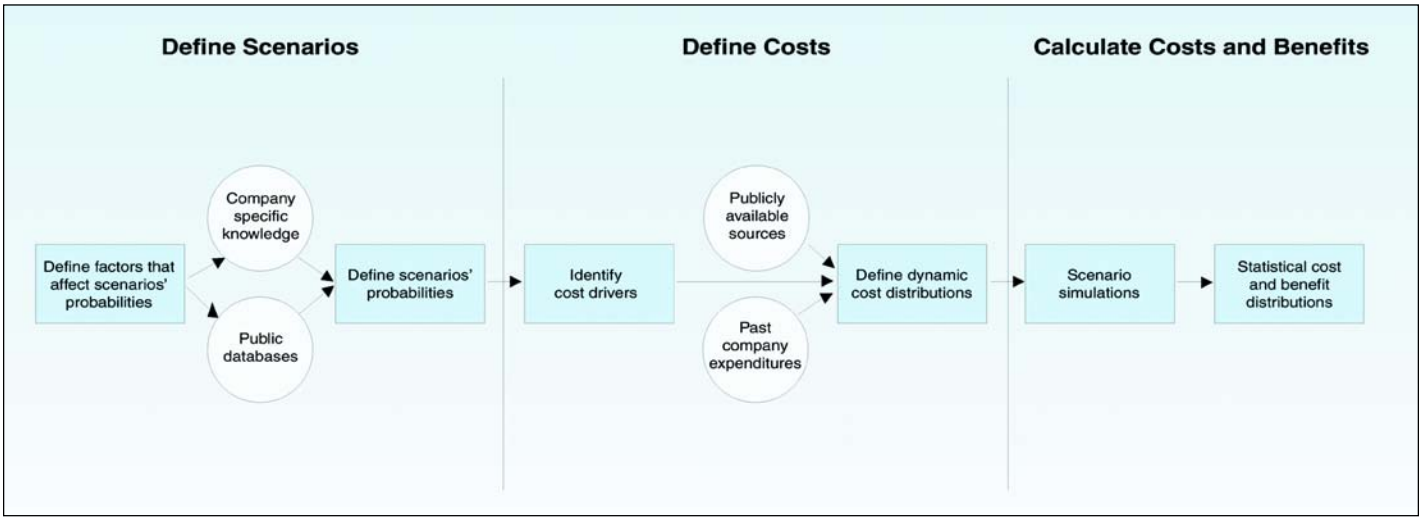

Figure 1. The TCA process defines scenarios and their costs in a methodical manner.

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Cost Type	Example	Data Source
III: Future and Contingent Liability	Civil and criminal fines and penalties	EPA's Integrated Data for Enforcement Analysis (IDEA) database; National Compliance Database
	Cost of accidents	EPA ARIP database
IV: Intangible - Internal	Staff (productivity/morale; turnover; union negotiating time)	Industry-specific studies estimating medical costs and lost wages from workplace injuries
	Market share (value chain perception, public perception, consumer perception)	Studies regarding the costs associated with loss of market share due to changes in public perception associated with industrial accidents
V: External	Pollutant discharges to ground water	Natural resource damage (NRD) settlements for ground water contamination
	Natural habitat impacts: local community	Published literature on willingness-to-pay scales, related to preservation of natural habitat or to protection of a particular species. Also, data on costs of restoring habitats or species.

Table C. Selected Cost Databases in TCA Methodology.

have demonstrated the importance of bringing together a multidisciplinary team of domain experts from across the company to participate in the brainstorming and reality-checking that a TCA analysis entails (Step 3 and Step 5 below). These applications have shown that the insight generated by the team during a structured and interactive TCA process far exceeds that which could come from the individuals working separately.

Steps in the TCA Methodology

1. *Goal Definition and Scoping.* Define the project and purpose of the TCA analysis.

2. *Streamline the Analysis.* Define the relevant activities within the analysis that may influence the decision.

3. *Identify Potential Risks.* Define alternatives, each of which can have numerous risk/cost scenarios. Specify the cost drivers (e.g. compliance obligations and remediation costs). Evaluate the relative importance of impact categories and the feasibility of collecting cost data for them.

4. *Conduct Financial Inventory.* Calculate Type I, II, III, IV, and V costs. Type I and II costs are derived from a company's internal cost accounting system. Type III to V costs incorporate probability, frequency of occurrence, and timing of occurrence for important cost categories where relevant data are available - *Figure 1*.

5. *Conduct Impact Assessment.* Review the costs to determine which are the most significant, and assess how that information can be best incorporated into the decision-making process.

6. *Document Results.* Document the assumptions and results for each scenario and cost decision, especially for important potential impacts that are not currently feasible to cost.

7. *Feedback to Company's Decision Loop.* Evaluate the TCA results as part of the company's main decision process.

The final step -- feedback -- recognizes that the TCA is only one input to an overall process that needs to include many types of information.

The steps in the TCA are repeated as needed. The third step, in particular, may require several discussions to determine how to identify risks and costs within a certain scenario. Each alternative must be detailed prior to the actual costing and analysis functions.

The financial inventory for contingent, intangible, and external (Type III, IV, and V) costs may seem daunting, due to uncertainties in the magnitude of the cost and the probability of occurrence. To ease the chore, the task force compiled several cost databases and descriptions of how some cost values could be represented;[4] Table C shows a few examples. The TCA methodology also allows users to enter company-specific data (for example, a company's past fines and penalties). CWRT is currently sponsoring projects to develop more data for external societal (Type V) costs, which will further enhance the usefulness of TCA.

The task force also developed tools to support the implementation of the TCA methodology. The TCA methodology report[4] includes manual tools for data gathering. Checklists ensure that the project scope identifies corporate goals and other critical project constraints. In addition, cost spreadsheets ensure that a comprehensive set of EHS costs are represented. These also provide summary locations for cost items and comment fields for documenting the analysis assumptions.

These manual assessment tools work well for well-defined costs. As the number of uncertainties, scenarios, and alternatives multiplies, and the need for in-depth analysis of cost drivers increases, the additional complexity is best handled with a dedicated software application.

Specialized software, including a scenario builder that can integrate inputs and ideas from company-wide cross-functional teams of experts (Figure 2), expands on the manual method by using Monte Carlo probability techniques to calculate contingent, intangible, and external (Type III, IV, and V) costs during the financial inventory. The software,[7] developed for use during the CWRT collaboration, analyzes the costs and benefits using a range of financial calculations that conform to standard industry practice for economic evaluations and corporate accounting conventions. It also provides extensive features for building and managing databases of costs and project information.

TCA Analysis Example

A simple example can show how TCA methodology could be applied to a real world decision. In this example, a company

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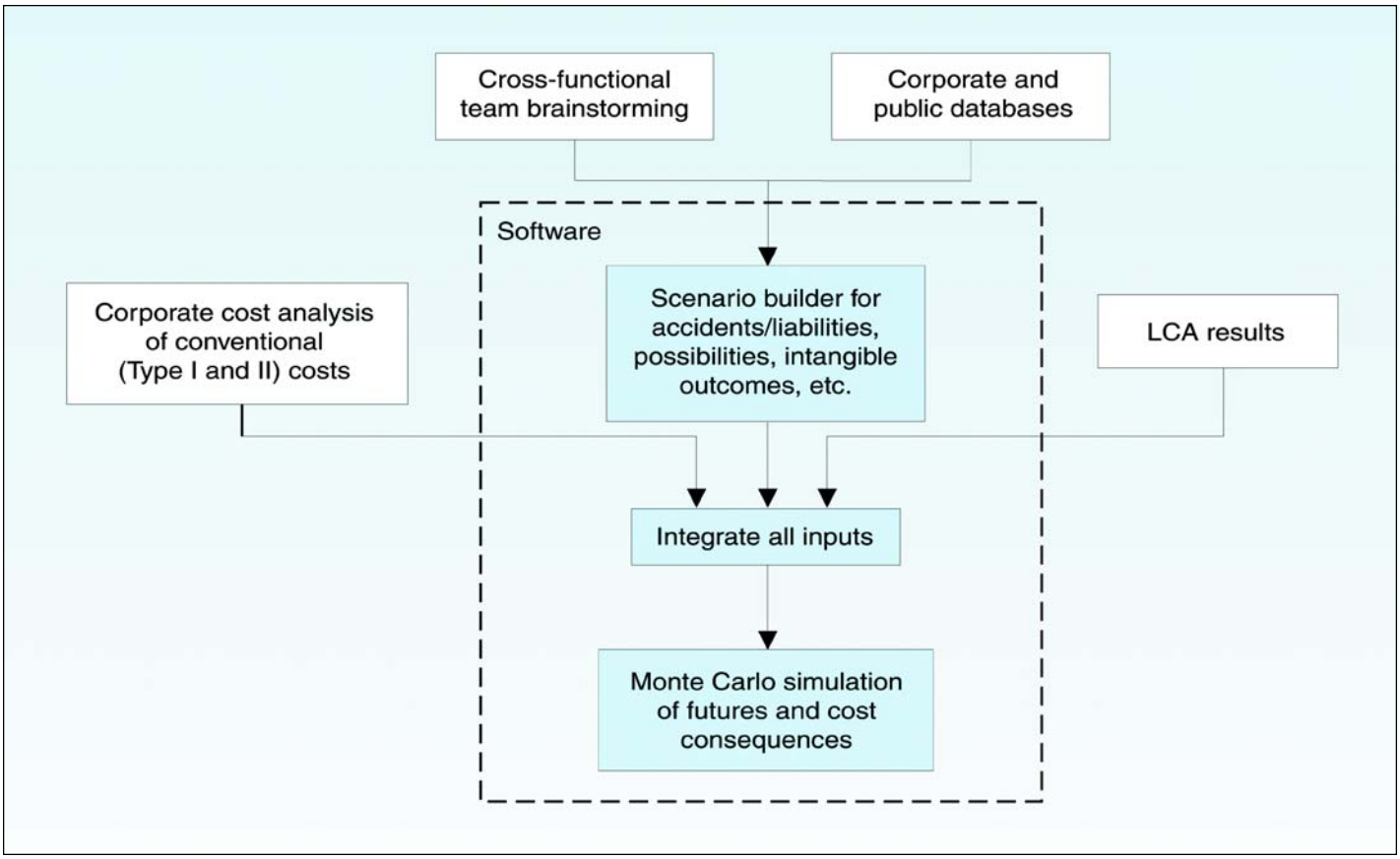

Figure 2. The software integrates conventional cost data and LCA results with a scenario builder. Company inputs are shown in white, and software functions are shown in blue.

has several goals aimed at reducing waste generation from its industrial process. Currently, the company produces two waste streams, as shown in Figure 3 - liquid hazardous waste (Stream 1) and aqueous sludge (Stream 2). In Step 1, *Goal Definition and Scoping*, the goal is to decide which waste stream will receive research and development funding for waste reduction.

Waste Stream 1 is currently incinerated on-site and Waste Stream 2 is land filled off-site. Although Figure 3 illustrates other waste treatment options, in Step 2, *Streamline the Analysis*, the cross-functional team decides to focus the analysis only on the waste disposal options currently used for the two streams.

During Step 3, *Identify Potential Risks*, the team brainstorms risk scenarios for both waste streams. For each risk scenario, the group defines three items:

1. the probability of the scenario occurring

2. the consequence(s) that will be realized if the scenario occurs

3. the cost that will be incurred for each consequence

For example, one scenario states that a new air emission standard will take effect in the next year - *Figure 4*. The scenario's probability is 100%, the scenario's consequence is a one-time capital investment in equipment (Type III, environmental compliance), and the cost of the equipment is $1.2 million at the end of Year 2.

Continuing the process, the team develops additional scenarios for Waste Stream 1 and similar scenarios for Waste Stream 2.

The team next completes Step 4, *Conduct Financial Inventory*. To begin the inventory, the company's accountants provide direct and indirect (Type I and II) costs. The software's ability to work with probabilistic scenarios allows the team to handle contingent, intangible, and external (Type III, IV, and V) costs in a manner consistent with direct and indirect costs. For each risk scenario, the team calculates a total present value cost over a three-year evaluation period by using CWRT cost databases and the company's own previous experience. Table D and Table E show TCA results for both waste streams, based on a fully developed set of scenarios for both waste streams. For simplicity, this example does not include intangible external costs (Type V), which are borne by society and not directly by the company. (The CWRT methodology report includes a fully developed analysis of Type V costs.)[2]

Once the financial inventory is complete, the team proceeds to Step 5, *Conduct Impact Assessment*, to analyze the results. Based only on direct and indirect (Type I and II) costs, Waste Stream 1 appears to be the more costly disposal method. In the third year, however, the analysis quantifies the potential impact of an unauthorized disposal activity. This future liability weights the results so that Waste Stream 2 could be more costly. In the real world, the TCA would be reviewed again to reassess both the probability of the occurrence and the uncertainties in the cost magnitude. If external (Type V) costs are included, the company must determine how to use those costs in the decision-making.

Following the analysis, the team completes Step 6, *Document Results*, and Step 7, *Feedback to Company's Decision*

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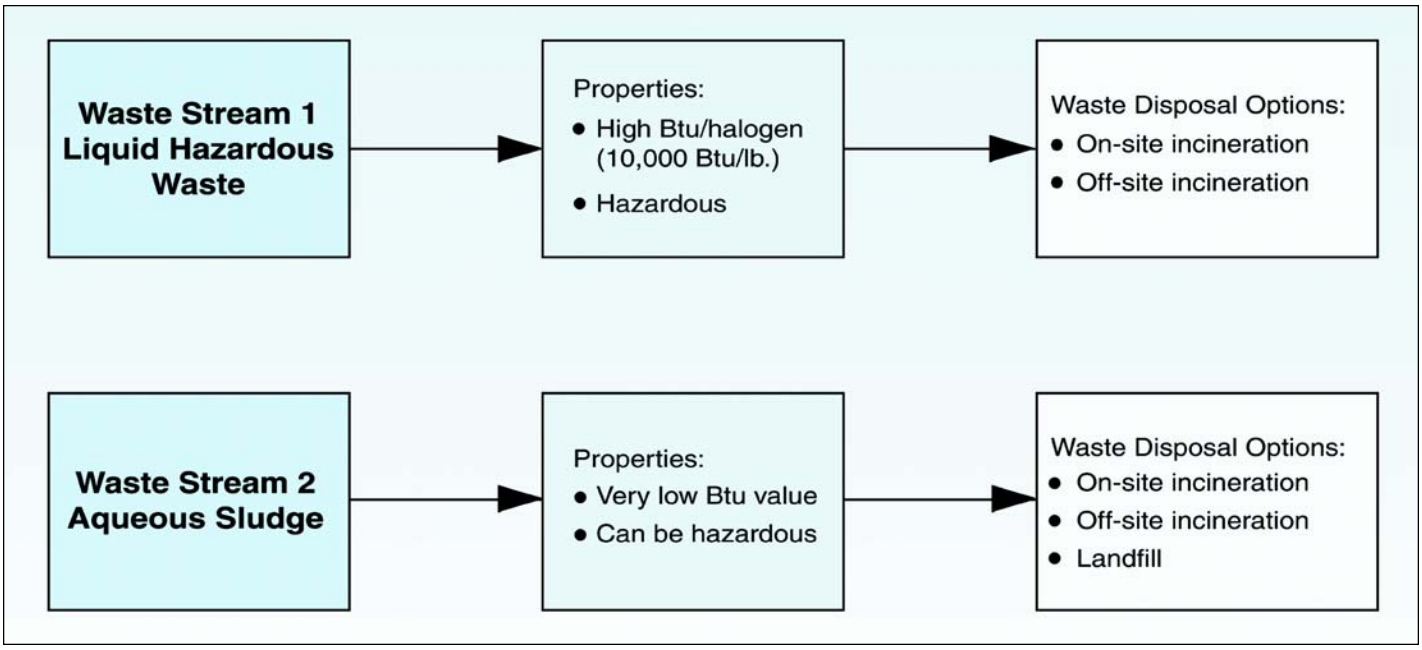

Figure 3. The hypothetical company produces two waste streams.

Loop. Based on these results, the company may immediately apply resources to reduce costs of Waste Stream 2. They may develop a longer-term plan to investigate Waste Stream 1. The information provided by the TCA leads to improved discussion of environmental costs and more detailed long-term planning for waste reduction.

Benefits of TCA

As the example shows, the TCA methodology is specifically designed for internal managerial decision-making. TCA can provide the costing framework for decisions about process development, product mix, waste management, pollution prevention, facility location and layout, outbound logistics, and other business-wide issues. Using TCA allows a business to better control overhead costs and to obtain more accurate estimates of the cost of products and services. Information provided by TCA also improves risk assessment and management.

The companies on the CWRT task force tested both the TCA methodology and the software, and the lessons learned during early testing were incorporated into both the final methodology and the software application.

The Dow Chemical Company was one of the first to begin pilot programs using TCA. A key step for implementing TCA was integrating it into existing company work processes. Dow's solution was to hold one- to two-day multifunctional workshops, creating multifunctional teams of key business and project people. Each workshop analyzed a specific issue within one of Dow's internal businesses. The workshops focused only on Type III and IV costs since conventional accounting methods already accounted for Type I and II costs. The workshops did not address Type V costs, due to lack of economic metrics for externalities. To distinguish their abbreviated internal method from the full TCA methodology, Dow dubbed their application "Total Business Cost Assessment" or "TBCA."

Dow has completed approximately 40 TBCA projects to date. Some of these related to Dow's Environmental, Health, and Safety Goals for 2005, which includes voluntary aggressive plans to improve the company's EHS performance and to reduce air and water emissions for global operations.[8] Project workshops focused on specific issues such as wastewater and transportation. The projects strove to determine the total benefit of EHS 2005 goal implementation, while determining a fuller cost/benefit basis for EHS improvements. A detailed discussion on how Dow implemented these projects will be presented in an upcoming edition of *Environmental Progress*. Another TCBA pilot looked at the "soft" (Type III and IV) economic benefits of a potential acquisition product. Based on the results from their TBCA projects, Dow feels that TCBA is a good way to quantify EHS value and is integrating the methodology into their business practices.

Dow's experience was typical of the testing performed at other companies on the AIChE task force, such as Monsanto, Eastman Chemical, and GlaxoSmithKline. These companies have already seen TCA's benefit on their decision-making processes. One company used TCA to compare a naturally occurring product to an artificially created product. Another company evaluated methods for delivering different forms of a product to a customer. These companies are encouraged by TCA's potential for reducing overall costs, which will improve their competitive position within their marketplace.

Total Cost Assessment methodology provides a standardized approach to identifying costs and benefits associated with Environmental, Health, and Safety issues for industrial products and processes. The methodology serves as a means for integrating information and judgments from across the company, aiding the company's managers in making informed decisions about Environmental, Health, and Safety opportunities and impacts, and contributing to improved long-term competitiveness.

References

1. The Center for Waste Reduction Technology (CWRT) helps industry develop tools and methodologies supporting sustainable manufacturing practices and environmental stewardship.

2. Deutsch, Claudia H. "Together at Last: Cutting Pollution

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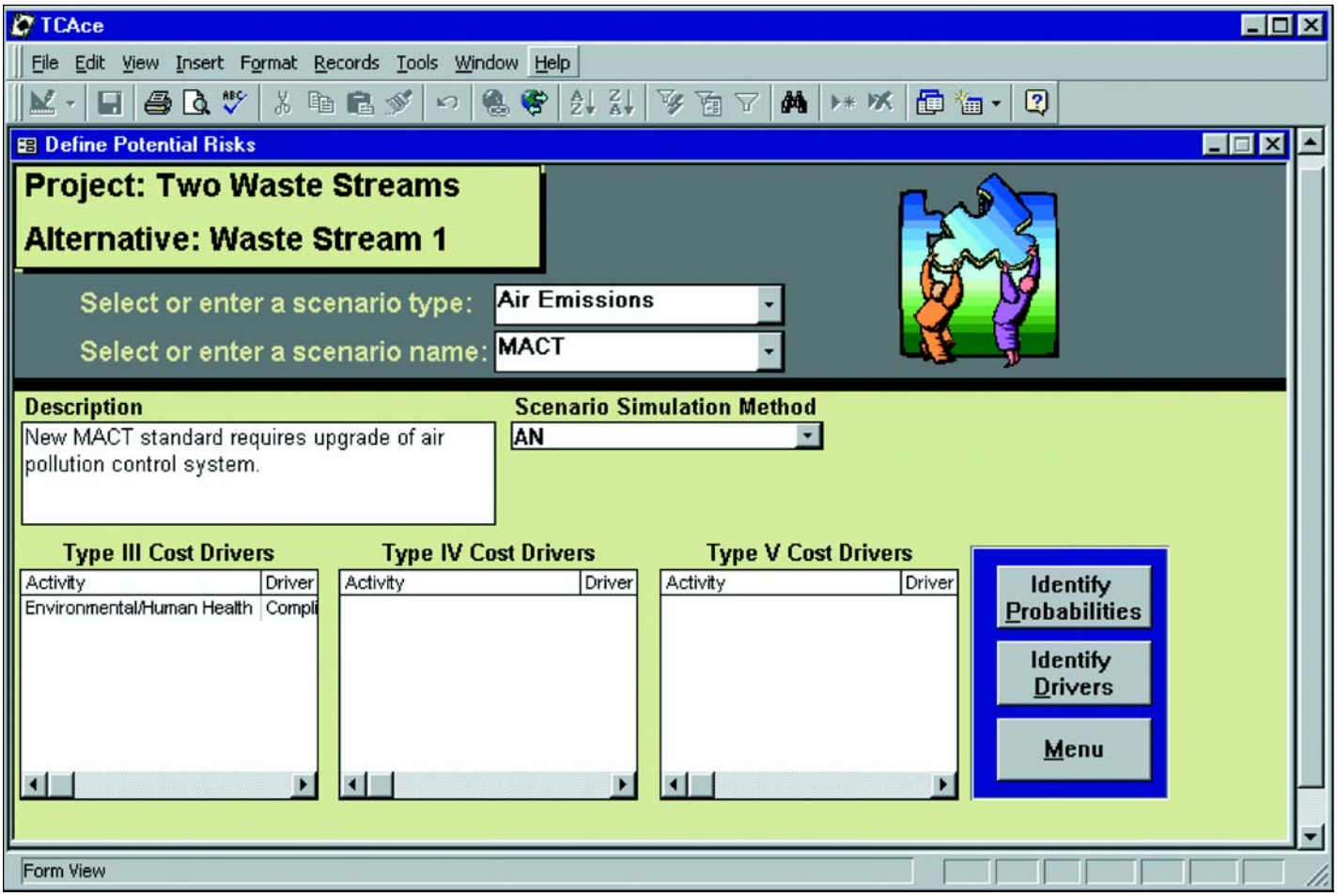

Figure 4. The software's scenario builder combines probability.

and Making Money." *The New York Times*, September 9, 2001.

3. GlaxoSmithKline was SmithKline Beecham at the time of the study.

4. CWRT 1999: Total Cost Assessment Methodology. Center for Waste Reduction Technologies, American Institute of Chemical Engineers, New York, NY. (Available for download at http://www.aiche.org/cwrt/projects/cost.htm.)

5. American Petroleum Institute (API). 1989. Measuring Natural Resource Damages: An Economic Appraisal. API Publication No. 4490.

6. Mundy, B and D McLean. 1998. Using the Contingent Value Approach for Natural Resource and Environmental Damage Applications. The Appraisal Journal, July 1998:290-297.

7. Information is available at www.TCAce.com.

8. The Dow Chemical Company's Goals for 2005 are explained on the Company's Web site, http://www.dow.com/environment/goal2005.html.

Cost Type	Year 1	Year 2	Year 3	Present Value Totals
Type I and II	4.0	3.57	3.2	**$ 10.77**
Type III				
Scenario 1 New air pollution standard	----	1.07	0.94	**2.01**
Scenario 2 Incinerator non-compliance	----	0.027	0.012	**0.039**
Scenario 3 Waste reduction	----	----	0.24	**0.24**
Type IV				
Scenario 2 Client relationships	----	----	0.24	**0.24**
Totals	4.0	4.67	4.63	**$ 13.30**

Table D. Cost Analysis for Waste Stream I ($ in Millions).

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Cost Type	Year 1	Year 2	Year 3	Present Value Totals
Type I and II	3.0	2.68	2.4	**$ 8.08**
Type III				
Scenario 1 Price rise at landfill	----	----	0.44	**0.44**
Scenario 2 Transportation spill	0.012	0.011	0.01	**0.033**
Scenario 2 Penalty for spill	0.003	0.002	0.002	**0.007**
Scenario 3 Transporter illegally dumps	----	----	7.12	**7.12**
Scenario 4 Label and manifest fines	0.0001	----	----	**0.0001**
Type IV				
Scenario 5 Worker morale low	----	----	2.0	**2.00**
Totals	3.02	2.69	11.97	**$ 17.68**

Table E. Cost Analysis for Waste Stream 2 ($ in Millions).

About the Author

Joseph E.L. Rogers, ScD was appointed Director of the American Institute of Chemical Engineers' (AIChE) Center for Waste Reduction Technologies (CWRT) at the end of 1997. In his varied industrial career, Dr. Rogers has served in a number of positions with the Halcon SD Group and Scientific Design Company, including the positions of president and COO. He also was president and CEO of Chemap, Inc. (Alfa-Laval, Inc.), as well as of several smaller entrepreneurial businesses. Dr. Rogers holds a BS from the University of Edinburgh, Scotland, and an MS and ScD from the Massachusetts Institute of Technology, all in chemical engineering. He did additional coursework at the Alfred P. Sloan School of Management. A member of AIChE since 1971, Dr. Rogers is also a member of the American Chemical Society, Sigma Xi, and the UK's Institution of Chemical Engineers.

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This article gives a preview of the ISPE Packaging and Warehousing Baseline® Guide which is currently under development.

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Baseline® Pharmaceutical Engineering Guide Series Update: A Preview of Packaging and Warehousing (Draft)

by Nancy St. Laurent and Mark von Stwolinski

The Packaging and Warehousing Baseline® Guide will be the seventh Guide in ISPE's Baseline® series. The Guide will cover, in detail, those topics related to packaging and warehousing which are touched upon by other Baseline® Guides.

The Guide will be broken down into two distinct sub-guides: one for packaging and one for warehousing. The packaging portion will identify primary, secondary, and tertiary packaging operations. The primary operations will not include those covered under other Guides that have been published, such as the Sterile Manufacturing Facilities Baseline® Guide. The warehousing portion will identify incoming materials, in-process materials, and shipment of goods. Facility planning, flow of materials, utilities, environment, and equipment operations also will be covered in both sections.

Regulatory considerations including GMPs, OSHA, EPA, and other regulations will be addressed for all packaging and warehousing operations. This Guide will examine equipment, integration, architectural, and MEP considerations. Technology transfer from manufacturing also will be addressed.

A tentative outline is presented below. This is the basis of the Chapters in the Guide and is subject to change as the draft progresses.

Packaging

This outline proposal organizes the packaging part of the Guide around the three distinct functions of primary, secondary and tertiary packaging. This grouping will facilitate the efforts of all users in designing these spaces. The Task Team also is considering organizing this by product dosage form as an alternative.

1. Introduction

1.1 **Background** (the modern packaging facility)

1.1.1 The design, construction, commissioning, and validation of packaging facilities can pose challenges for operations, design professionals and equipment suppliers. In some cases, these facilities are required to meet cGMP requirements while remaining in compliance with all other governing codes, laws, and regulations.

1.1.2 The goal is to establish consistent guidelines that can be incorporated into the design of these facilities.

1.1.3 This Guide was prepared by ISPE with feedback from industry representatives from all disciplines, and comments provided by the FDA.

1.1.4 This Guide recognizes that industry standards evolve over time and this Guide reflects the current understanding of these standards at the time of publishing.

1.1.5 This Guide encourages innovative approaches to designing a basic cGMP Packaging facility.

1.2 **Scope**

1.2.1 This Guide may be used by industry for the design, construction, and commissioning of new packaging facilities.

1.2.2 This Guide focuses on the facility design issues for primary packaging for non-sterile products and secondary and tertiary packaging for all pharmaceutical and biologic products. Examples of dosage forms where primary packaging will be addressed include:

- 1.2.2.1 Powders
- 1.2.2.2 Tablets Bottling and Blister Filling
- 1.2.2.3 Liquids Filling (Non-Sterile)
- 1.2.2.4 Inserts: Rectal, Vaginal, Optical (Medicated Contacts)
- 1.2.2.5 Transdermal
- 1.2.2.6 Ointments and Creams
- 1.2.2.7 Other Unique Dosage Forms not covered above

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1.2.3 This Guide is intended primarily for facilities regulated by the FDA that supply the United States (US) Clinical Trials and commercial markets and follow US standards and references. The emerging ICH requirements may be referred to in the Appendix.
1.2.4 The concepts proposed constitute a baseline from which to proceed with the design.

1.3 **Key Features of this Guide**
1.3.1 The risk of product exposure and the level of protection during primary packaging for non-aseptically produced products are addressed. For parenteral products, refer to the ISPE Baseline® Guide Volume 3 - Sterile Manufacturing Facilities.
1.3.2 Primary packaging is the area of overlapping requirements for manufacturing and packaging.
1.3.3 Good engineering practice should be applied to the facility design and layout.
1.3.4 This Guide addresses the baseline GMP requirements for an economical facility.
1.3.5 Discretionary, non-GMP, owner elected facility, and equipment upgrades can be an opportunity to optimize the packaging process and to present the facility to visitors: FDA, employees, corporate partners, etc.
1.3.6 How to Use this Guide:
1.3.6.1 Review equipment selection based on volume throughput, costs, product diversity, expansion, and manual versus automation philosophy.
1.3.6.2 Understand the cost and benefit trade-offs for regulatory compliances.
1.3.6.3 Identify the cost and benefit trade-offs for discretionary upgrades to optimize the process and or the facility.
1.3.7 Chapter Overview Chart, Figure 1.1
1.3.7.1 This Guide for facility design is organized by the packaging step, i.e.: primary, secondary and tertiary packaging. Each of these areas has distinct facility requirements.

2. Concepts and Regulatory Philosophy

2.1 **Introduction**
2.1.1 Consistency and control of the packaging and labeling steps are essential to completing this phase of the product production sequence.
2.1.2 The areas of emphasis are primary product closure and the associated levels of protection, and product control and labeling for primary, secondary, and tertiary packaging.
2.1.3 Multi-product facilities may require rapid product changeovers and line clearances.
2.1.4 Note: the following items are from the OSD Guide because primary packaging needs manufacturing supportive text for facility design criteria.
2.1.5 Product Exposure: Open versus Closed; if open, then…
2.1.6 Critical Parameters: a critical parameter is a processing parameter (e.g. filling hygroscopic powders) that affects product quality, efficacy, or stability.
2.1.7 Product Level of Protection: e.g. bottling coated tablets may not need the same room environment as 2.1.6 above.
2.1.8 Product Protection Factors: why the difference between the two above.
2.1.9 Required Extent of Validation: Systems are considered critical and should be validated when they either are in direct physical contact with the drug or used to measure, monitor or record a critical parameter, e.g. humidity control for filling hygroscopic powders.
2.1.10 Design Conditions versus Operating Ranges:
2.1.11 *Figure 2.1 Packaging Criteria Chart*

2.2 **Product Exposure**
2.2.1 Describe here or refer them to the OSD Guide.

2.3 **Critical Parameters**
2.3.1 Describe here or refer them to the OSD Guide.

2.4 **Product Level of Protection**
2.4.1 Describe here or refer them to the OSD Guide.

2.5 **Product Protection Factors**
2.5.1 Describe here or refer them to the OSD Guide.

2.6 **Required Extent of Validation**
2.6.1 Describe here or refer them to the OSD Guide.

2.7 **Design Conditions versus Operation Ranges**
2.7.1 Describe here or refer them to the OSD Guide.

3. Primary Packaging

3.1 **Introduction**
3.1.1 Provide recommended baseline practices for primary packaging.
3.1.2 Provide points to consider for design and line integration.

3.2 **Unit Operations**
This section will identify the different unit operations required for the product dosage forms, i.e. tablet, blister line, followed by bottling of blisters, cartoning, or other packaging, labeling, etc.

3.3 **Process Equipment Considerations**
This section will discuss the various equipment options for the above operations and the facility requirements necessary for installation and efficient and safe operations.

3.4 **Line Integration Considerations**
Conveyors, controls, changeover criteria, product accumulation all are critical areas that need to be considered when building a new packaging facility.

3.5 **Architectural and Layout**
3.5.1 Design Criteria
3.5.1.1 The facility layout should be an integrated design that satisfies process and equipment layout requirements.
3.5.1.2 More from OSD Guide
3.5.2 Product and Material Flow
3.5.2.1 More from OSD Guide
3.5.3 Personnel Flow
3.5.3.1 Gowning
3.5.3.2 Personnel Protection

3.6 **HVAC**
3.6.1 Process Definition
3.6.2 Critical Parameters
3.6.3 Non-GMP Design Considerations

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Criteria	Primary Packaging	Secondary Packaging	Tertiary Packaging
Product Exposure	Open	Closed	Closed
Product Levels of Protection	Level 1 - General (N/A) Level 2 - Protected (possible) Level 3 - Controlled/Classified (typical)	N/A	N/A
Primary Concern	Sealing the Primary container and proper labeling	Protecting the Primary container from damage with Secondary Packaging. Ensure proper labeling.	Protecting the Secondary Package from Damage and ensure proper labeling.
Environmental	Manufacturing or almost Manufacturing Quality	Non-classified, but ensure packaging materials, paper, and label adhesives have a suitable environment.	Non-classified and suitable to protect shipper labels from degradation.

Figure 2.1. Packaging Criteria Chart.

3.7 **Utility Systems**
3.8 **Electrical Systems**
3.9 **Instrumentation and Controls**

4. Secondary Packaging
4.1 **Introduction**
4.1.1 Provide recommended baseline practices for secondary packaging.
4.1.2 Provide points to consider for secondary packaging.

4.2 **Unit Operations**
Similar to above.

4.3 **Process Equipment Considerations**
Similar to above.

4.4 **Line Integration Considerations**
Similar to above.

4.5 **Architectural and Layout**
4.5.1 Design Criteria for Secondary Packaging.
4.5.1 etc.

4.6 **HVAC**
4.7 **Utility Systems**
4.8 **Electrical Systems**
4.9 **Instrumentation and Controls**

5. Tertiary Packaging
5.1 **Introduction**
5.2 **Unit Operations**
5.3 **Process Equipment Considerations**
5.4 **Line Integration Considerations**
5.5 **Architectural and Layout**
5.6 **HVAC**
5.7 **Utility Systems**
5.8 **Electrical Systems**
5.9 **Instrumentation and Controls**

6. Commissioning and Qualification
This chapter will address the commissioning of the areas as well as touch upon the equipment commissioning and qualification. It will not go into detail on all the different types of equipment.

7. Other Considerations
This chapter will address other critical regulations that apply specifically to Packaging, such as OSHA, EPA, DEA, etc.

8. Definitions

9. Appendix

Warehousing

1. Introduction
1.1 **Background** (the modern warehousing facility)
1.1.1 The design, construction, commissioning, and validation of warehousing facilities can pose challenges for operations, design professionals, and equipment suppliers. In some cases, these facilities are required to meet cGMP requirements while remaining in compliance with all other governing codes, laws, and regulations.
1.1.6 The goal is to establish consistent guidelines that can be incorporated into the design of these facilities.
1.1.7 This Guide was prepared by ISPE with feedback from industry representatives from all disciplines, and comments provided by the FDA.
1.1.8 This Guide recognizes that industry standards evolve over time and this Guide reflects the current understanding of these standards at the time of publishing.
1.1.9 This Guide encourages innovative approaches to designing a cGMP warehouse in the pharmaceutical industry.

1.2 **Scope**
1.2.5 This Guide may be used by industry for the design, construction and commissioning of new cGMP warehousing facilities.
1.2.6 This Guide focuses on the facility design issues for incoming materials, quarantine, sampling, storage of in-process materials, storage and shipment of outgoing finished products. Examples of incoming materials include:
- 1.2.6.1 Raw Materials for Product Formulation
- 1.2.6.2 Packaging Materials - Non-Printed
- 1.2.6.3 Printed Packaging Materials
- 1.2.6.4 Office Supplies
- 1.2.6.5 Gases
- 1.2.6.6 Production Supplies, such as Gowns, Gloves, etc.
- 1.2.6.7 Testing Materials
- 1.2.6.8 All other Material Necessary for Plant Operations

1.2.7 This Guide addresses the warehousing requirements for sampling of all material that needs to be tested and released for use. This will include:

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1.2.7.1 Laboratory Test Materials
1.2.7.2 Raw Materials
1.2.7.3 Production Supplies
1.2.7.4 Packaging Supplies

1.2.8 This Guide will outline the storage requirements for quarantine, released materials, in process products, controlled product storage and finished goods. Returned product storage also is addressed.

1.2.9 This Guide is intended primarily for facilities that meet the FDA regulatory requirements in order to supply the United States (US) Clinical Trials and commercial markets and follows US standards and references. The emerging ICH requirements are referred to in the Appendix.

1.2.10 The concepts proposed constitute a baseline from which to proceed with the design.

1.3 **Key Features of this Guide**

1.3.8 The risk of product exposure and the level of protection during sampling of raw materials are addressed.

1.3.9 Warehousing is the key to the efficient flow of material into and out of the production facility.

1.3.10 Good engineering practice should be applied to the facility design and layout.

1.3.11 This Guide addresses the baseline GMP requirements for an economical facility.

1.3.12 Discretionary, non-GMP, owner elected facility, and equipment upgrades can be an opportunity to optimize the warehousing process and to present the facility to visitors: FDA, employees, corporate partners, etc.

1.3.13 How to Use this Guide;

1.3.13.1 Review selection of space, storage areas, racks, etc. based on volume throughput, costs, product diversity, expansion, and manual versus automation philosophy.

1.3.13.2 Understand the cost and benefit trade-offs for regulatory compliances.

1.3.13.3 Identify the costs and benefits trade-offs for discretionary upgrades to optimize the process and or the facility.

1.3.14 Chapter overview chart, Figure 1.1

1.3.14.1 This Guide for facility design is organized by the different activities that take place in a warehouse. Each of these areas has distinct facility requirements.

2. Concepts and Regulatory Philosophy

2.1 **Introduction**

2.1.12 Consistency and control of the warehousing operation is essential to completing this phase of the product production sequence.

2.1.13 The areas of emphasis are receiving and sampling of raw materials; quarantine of critical production items.

2.1.14 Multi-product facilities

2.1.15 *Note: the following items are from the OSD Guide because warehousing needs manufacturing supportive text for facility design criteria.*

2.1.16 Product Exposure: Open versus Closed

2.1.17 Critical Parameters: a critical parameter is a processing parameter (e.g., sampling hygroscopic powders) that affects product quality, efficacy, or stability.

2.1.18 Product Level of Protection: e.g., sampling printed materials may not need the same room environment as 2.1.6 above.

2.1.19 Product Protection Factors: why the difference between the two above.

2.1.20 Required Extent of Validation: Systems are considered critical and should be validated when they either are in direct physical contact with the drug or used to measure, monitor or record a critical parameter, e.g., humidity control for sampling filling hygroscopic powders.
Design Conditions versus Operating Ranges:

2.1.21 *Figure 2.1 Warehousing Packaging Criteria Chart*

2.2 **Product Exposure**
Describe here or refer them to the OSD Guide.

2.3 **Critical Parameters**
Describe here or refer them to the OSD Guide.

2.4 **Product Level of Protection**
Describe here or refer them to the OSD Guide.

2.5 **Product Protection Factors**
Describe here or refer them to the OSD Guide.

2.6 **Required Extent of Validation**
Describe here or refer them to the OSD Guide.

2.7 **Design Conditions versus Operation Ranges**
Describe here or refer them to the OSD Guide.

3. Receiving of Production Materials

3.1 **Introduction**
Provide recommended baseline practices for receiving of production materials.
Provide points to consider for design of storage, quarantine and sampling areas.

3.2 **Architectural and Layout**
Design Criteria
The facility layout should be an integrated design that satisfies process and equipment layout requirements
Product and Material Flow
Personnel Flow
Personnel Protection

3.6 **HVAC**
3.6.4 Process Definition
3.6.5 Critical Parameters
3.6.6 Non-GMP Design Considerations

3.7 **Utility Systems**
3.8 **Electrical Systems**
3.9 **Instrumentation and Controls**

4. Storage of In Process Materials

4.1 **Introduction**
4.1.3 Provide recommended baseline practices for storage of in process materials.

4.5 **Architectural and Layout**
4.5.3 Design Criteria for warehousing storage
4.5.4 Personnel Flow
4.5.5 Material Flow

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Criteria	Receiving and Sampling of Materials	Storage of Materials and Products	Distribution of Finished Goods
Product Exposure	Open	Closed	Closed
Product Levels of Protection	Level 1 - General (N/A) Level 2 - Protected (possible) Level 3 - Controlled/Classified (typical)	N/A	N/A
Primary Concern	Opening the contained for sampling. Area should be controlled for dust collection.	Protecting the Products. Ensure proper labeling to eliminate mix-ups.	Protecting the Package from damage and ensure proper labeling.
Environmental	Non-classified, but should be temperature controlled. Areas for quarantine may require humidity control as well.	Non-classified, but ensure packaging materials, paper, and label adhesives have a suitable environment.	Non-classified and suitable to protect shipper labels from degradation.

Figure 2.1. Warehousing Packaging Criteria Chart.

4.6 **HVAC**
4.7 **Utility Systems**
4.10 **Electrical Systems**
4.11 **Instrumentation and Controls**

5. Distribution of Finished Goods
5.1 **Introduction**
5.5 **Architectural and Layout**
5.6 **HVAC**
5.7 **Utility Systems**
5.8 **Electrical Systems**
5.9 **Instrumentation and Controls**

6. Commissioning and Qualification

7. Other Considerations

8. Definitions

9. Appendix

About the Authors

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Mark von Stwolinski, Principal, Dowler-Gruman Architects, is a contributor to the Guide and was instrumental in developing this outline.

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A Study of Upper-Extremity Myoelectric Prosthetics and Their External Power Sources

by Chris Moseley

The field of upper-extremity myoelectric prosthetics is being electronically advanced more each day. With this rapid advancement in technology, there are many challenges including finding an adequate power source to operate these devices without inconveniencing the patient. This article will discuss several products on the market attempting to address this problem.

This paper was presented at the 2001 ISPE Annual Meeting in Las Vegas as part of the Student Poster/ Paper Competition held annually by the Society. Chris Moseley, a student at the University of Missouri-Kansas City, was one of eight contestants in the annual contest. Previous to the Annual Meeting competition, Moseley was runner up at the ISPE Midwest Chapter local competition in mid-September.

The field of upper-extremity prosthetics has evolved tremendously in the past 10 years. It has gone from hibernating in the Dark Ages to showing the world the wave of the future. With this rapid advancement; there are many difficult obstacles to overcome. One of the most glaring complications is finding an adequate power source to operate the newer myoelectric models in the market place today. This paper will shed light on why this is such a difficult hurdle to overcome by giving a brief background of upper-extremity prosthetics and then a critical analysis of the new myoelectric prosthetics and their various power sources.

In the beginning, there were only passive prosthetics. This type of prosthesis is very stiff and not very functional. Passive prosthetics are primarily used for cosmetic purposes - to "fill a sleeve." They are attached to the body using some sort of harness system to hold the prosthesis in place. Due to the lack of mobility and function of these passive type prosthetics, the industry felt that it had to move forward and produce a more functional and practical device to better serve the patient which led to the body powered prosthesis.

Body powered prosthetics are still widely used due to there relatively inexpensive cost. They, like the passive prosthetics, are also mounted to the body with a harness system for stability. This type of prosthesis consists of a joint, such as an elbow, installed in the prosthesis. The patient is able to use this joint by manipulating their gross body movements to make the elbow perform in the correct manner. It is easily seen how this exaggerated sort of motion could lead to unwanted side effects to the patient. After several case studies, the practitioners discovered that this type of prosthesis causes various medical complications such as: muscle degeneration from overuse of the sound limb, Carpal Tunnel Syndrome, chaffing from the prosthesis rubbing against the skin in an unusual way, and decrease in the range of motion of the residual limb possessing the prosthesis due to the restrictive harness placed on the body. Even with the possibility of all of these side effects, these prosthetics are a popular option because of their increased functionality and inexpensive cost as mentioned before. With these adverse side effects in mind, engineers were employed to design some sort of device that would provide even more functionality than the body powered prosthetics and reduce the severity of the possible medical complications. This gave birth to the idea of myoelectric prosthetics.

The benefits of a myoelectric prosthesis far outweigh those of a body powered prosthesis. The most significant advantage to having a myoelectric prosthesis is the increased mobility and comfort for the patient. Instead of using a harness system, most myoelectric prosthetics use an advanced suction device to make the prosthesis adhere directly to the skin. This eliminates the restricted range of motion incurred with the body powered prosthetics. Another substantial advantage is that with this new suction type fitting, the rubbing of the prosthesis against the skin is alleviated. Finally, since myoelectric prosthetics are externally powered, the patient is not forced to contort their body near as much as was the case with body powered prosthetics.

The best explanation of how myoelectric prosthetics operate can be found in the words of Patel, Allen, and Rapach:

> *"The particular area of interest is the pyramidal system which functions by initiating and patterning movements. The pyramidal system is found to communicate with the rest of the body through the nervous system. The primary building blocks of the nervous system are neurons, of which there are about 10 billion in the human body. Their function is to transmit impulses from the central nervous system to the rest of the body. Nerve tissue is termed excitable since it may be stimulated by*

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electrical, mechanical, and chemical processes that in turn cause electrical signals to occur in milliseconds with amplitudes in the millivolts. When the nerve ending detects the signal, it triggers a chemical reaction which causes the fiber elements of the muscle to either contract or expand, resulting in limb movement. The myoelectric (EMG) signal is the result of this process and can be measured on the surface of the skin" (Patel, et al).

The measurement on the surface of the skin that Patel and company speak of is taken by several small electrodes placed on the inside of the prosthesis that press against the patients skin picking up the trace millivolt output of the nerve tissue. Finding the correct location to place those electrodes can be a very complicated and tedious task. The procedure used in most instances today is trial and error. The practitioner will sit down with the patient and connect several electrodes coming from his computer to the patient's residual limb. A program called Myoboy will measure the various potentials generated by the patient's movements and the practitioner will decide which electrode sites will send the best signal to the electrode. Keep in mind that the best output is not necessarily the strongest signal due to the nature of the device, which will be discussed later. After the sites have been determined, this information is conveyed to the engineer who will then design a very specific control unit for that patient.

These designs are made to meet certain specifications, which will vary from patient to patient. With the increased use of digital technologies, this process is becoming more sophisticated and refined as opposed to the older analog analysis. The most common way for the engineer to start the task of analyzing the signal is to eliminate the unwanted frequency components due to the patient's heart rhythm and the noise created from the electrode rubbing against the skin. The next step is to feed this filtered signal through a 20,000 times amplifier and then through a rectifier circuit. Finally, after the proper filtering and amplification has been done the signal is digitized (Patel).

Using this digitized signal, the engineer programs a microcontroller to control the prosthesis in a patient friendly way. Take into consideration a very sophisticated electronic elbow system. One such set-up the engineer could use could be that an input from a bicep contraction causes the arm to come up, and an input from a tricep contraction causes the arm to go down. To set-up the proper microcontroller the engineer must establish some sort of minimum voltage threshold value for reference. When the patient contracts his or her bicep, the voltage output must exceed the threshold for the arm to move up, and when the patient contracts his or her tricep the voltage output must exceed the threshold for the arm to move down. Most of these electronic elbow systems have a built in timer so that when the patients bicep and tricep voltage outputs are less than the threshold for exactly one second the elbow joint locks in place. At this time, to make the arm operate again, the patient must perform a cocontraction of the bicep and tricep. A cocontraction consists of both the bicep and tricep voltages exceeding the threshold at exactly the same time. This process is usually quite difficult for the patient considering the loss of muscle in the residual limb, which brings about the before mentioned importance of electrode placement. In most instances the strength in the residual limb bicep and tricep is not the same leading to different output potentials to the electrodes. In order for the patient to exhibit a proper cocontraction were both voltage levels exceed the threshold at exactly the same time, a proper ratio must be established so that the correct amplification of one or both of the muscles can be determined so as to allow the patient to properly control the arm. It is easy to see that a system of this nature would need some sort of power supply that would last long enough and supply enough power to operate the prosthesis for extended periods of time. This discussion leads to the relevance of external power source life and strength when dealing with myoelectric prosthetics (Mandacina).

There are four main types of external power sources being used in today's myoelectric prosthetics. They are Nickel-Cadmium batteries, Alkaline batteries, Lithium-Ion batteries, and high-capacity Lithium-Ion batteries. An in depth analysis of each of these four batteries will reveal that the most beneficial selection for power and endurance is the high-capacity Lithium-Ion battery.

The first battery to be analyzed is the Nickel-Cadmium battery. This battery ideally exhibits about 6 Volts potential and 500 mA current. The expected life is approximately three fourths of one day and recharges in approximately seven to eight hours. The down side of this type of battery besides its extremely long recharge time is that it has memory. When a battery is said to have memory, it refers to the storage cells contained within the battery. In a Nickel-Cadmium battery, which is the same type as in most cell phones, if the battery is not fully dissipated before it is recharged, some the cells within the battery are damaged and unable to be used again. This leads to loss of battery life each time the battery is recharged before it is fully dissipated causing the patient to purchase a new battery more often.

The second type of battery to be analyzed is the Alkaline battery. This type of battery is very affordable and very easy to find. The Alkaline batteries used in myoelectric prosthetics are standard 9 Volt potential like the ones available at any convenience store. They typically last about three to seven days depending on the use of the prosthesis. The advantages to this type of battery are its low cost and immediate availability. These batteries can be purchased at any convenience store, which makes them especially handy if the patient decides to leave the area where they are being treated. Not many convenience stores sell Nickel-Cadmium and Lithium-Ion batteries. The down side to the Alkaline battery is the cost over time. Imagine a man or woman in their twenty's needing a myoelectric prosthesis. The average price of a 9 Volt battery is approximately three dollars. Now think about how much money that person would have to spend throughout their lifetime to keep purchasing new batteries every three to seven days. Yes, there are rechargeable Alkaline batteries, but they have memory also, and take nearly 13 hours to recharge. This is obviously a costly route to take.

The third battery to be analyzed is the Lithium-Ion battery. This type of battery ideally supplies about 7.2 Volts potential and 750 mA current. This is probably the second best choice to make. Lithium-Ion batteries are memoryless, meaning that they will recharge to full strength every time even if the battery is not fully discharged. This adds convenience for the patient "on the go." They last approximately three days depending on use of the prosthesis before they require recharging (Mandacina).

The last type of battery to be analyzed is the high-capacity Lithium-Ion battery. This is by far the best choice. This battery supplies about fifteen percent more power than the standard Lithium-Ion battery and lasts nearly twice as long. This battery, like the standard Lithium-Ion battery, has no memory.

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> ***...a myoelectric prosthesis powered with a high-capacity Lithium-Ion battery. This is the most comfortable and convenient set-up possible in the market place today.***

Although the price is high, the benefits are far greater (LTI).

Conclusions

It has been shown that the best way to improve the quality of life of an individual needing an upper-extremity prosthesis is to fit that person with a myoelectric prosthesis powered with a high-capacity Lithium-Ion battery. This is the most comfortable and convenient set-up possible in the market place today.

References

1. "LTI - Liberating Technologies." Home page. Online. December 2001.

2. Mandacina, Steve. Personal interview. November 13, 2000.

3. Patel, Parimal, Allen, Sam, and Rapach, George. eds. San Antonio, TX 1988. Proceedings of the IEEE in Medicine and Biology Society 10th Annual International Conference. San Antonio, TX: University of Texas at San Antonio, 1988.

About the Author

Chris Moseley is an undergraduate student of electrical engineering with an emphasis in signal processing at the University of Missouri-Kansas City. Moseley has been researching the area of upper-extremity myoelectric prosthetics for approximately one year via a close working relationship with certified practitioners in the field. He plans to graduate in May of 2002 with a BSEE and a minor in mathematics. After completing his current degree program, Moseley plans on pursuing certification in the area of prosthetics and orthotics with the ambition of becoming one of the more technically advanced practitioners in the field today.

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Twenty Years of Experience in Powder Transfer Technology: Docking Stations, Vital Components in Bin Technology and Modern Plant Automation

This article presents the latest generation of docking stations which resolve the issue of powder transfer, under perfect GMP conditions, between clean production rooms and less clean technical areas.

by Willy J. Lhoest, PhD

Historical Background

Until 1982 and even today in older plants, products such as powder mixtures, granules, pellets, bulk tablets, and empty and filled hard gelatin capsules are currently stored during process, inside granulation rooms, tabletting rooms, capsule filling rooms, and in other words, inside clean production facilities.

In fact, production rooms are constructed larger than needed because they are used for the following dual purposes: a justified manufacturing function and a less justified storage function for the products, before and after processing. It is obvious that using clean production facilities for storage purposes is a luxury since they can be stored in warehouse-type zones if their container is perfectly tight.

For the first time in 1982, two Belgian pharmaceutical engineers,[1] designed and built a plant for SmithKline (now GlaxoSmithKline) in Spain where products were no longer kept inside the clean production rooms, but in so called "technical areas." - *Figure 1*. In this new con-

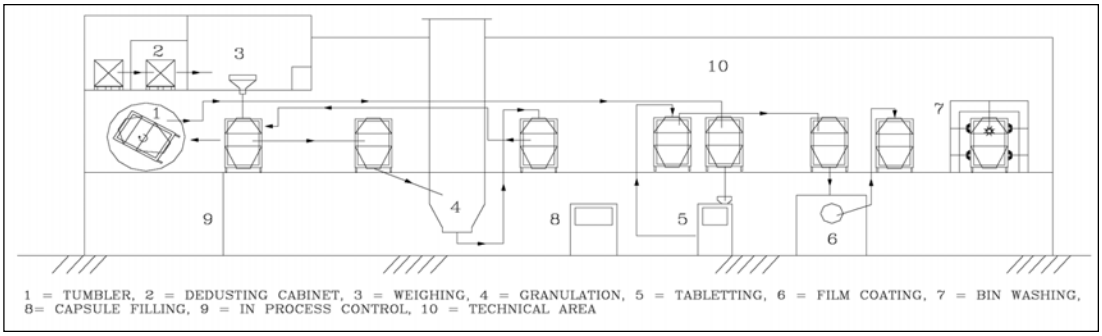

Figure 1. For the first time in 1982, in the SmithKline plant at Alcala de Henares, Spain, materials to be processed as well as materials having been processed by the production machine, were taken out of the production rooms and kept in tight containers in separate, technical areas.[1]

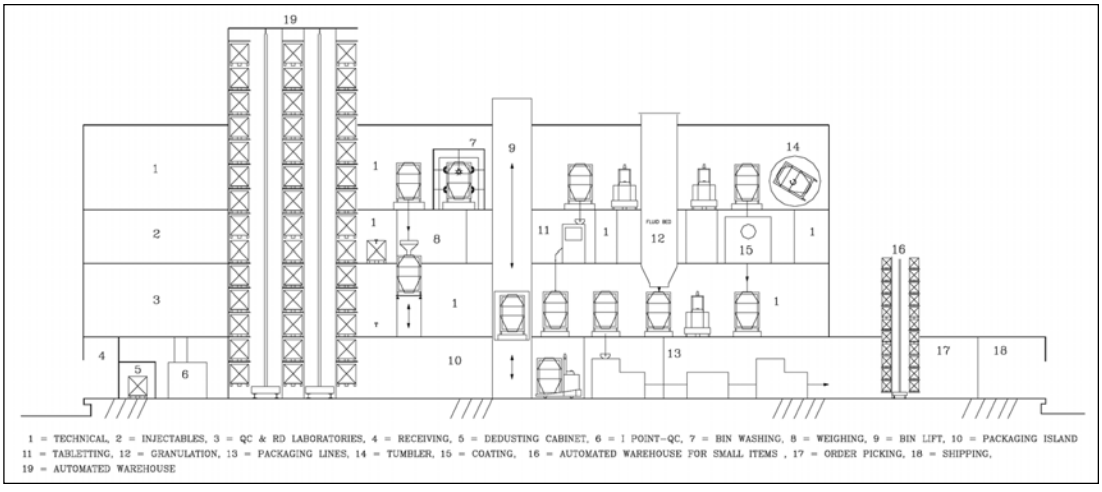

Figure 2. Basic concept for the Pharmachemie plant in Haarlem, The Netherlands. The original Alcala concept was further developed by adding a second technical floor below production and another packaging floor underneath. The gravity flow was thereby extended to 4 levels, served by wire guided vehicles (AGV) and connected to automated warehouses

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> ***Docking stations must handle the product transfer between clean production rooms and less clean technical areas, under tight and perfect GMP conditions.***

cept, clean production rooms are completely segregated from technical areas. Products feed the production machines from the technical area located on the floor above and are returned to said area, after each individual process step.

It is at this point in time that the terminology of "docking stations" was invented and introduced for the first time in the industry to designate the piece of equipment able to handle, under perfect GMP conditions, the product transfer between clean production rooms and less clean technical areas. More specifically, each docking station had to connect a tight stainless steel bin containing a product in bulk to a process machine, and transfer the product to said machine automatically under strictly controlled conditions or vice-versa.

Docking stations must handle the product transfer between clean production rooms and less clean technical areas under tight and perfect GMP conditions.

This fundamental change was the start for a new generation of pharmaceutical plants which included other very successful concepts, such as the full gravity flow, the multi-level construction, the full containment, the islands of manufacturing, automated materials handling, and computer assisted manufacturing.

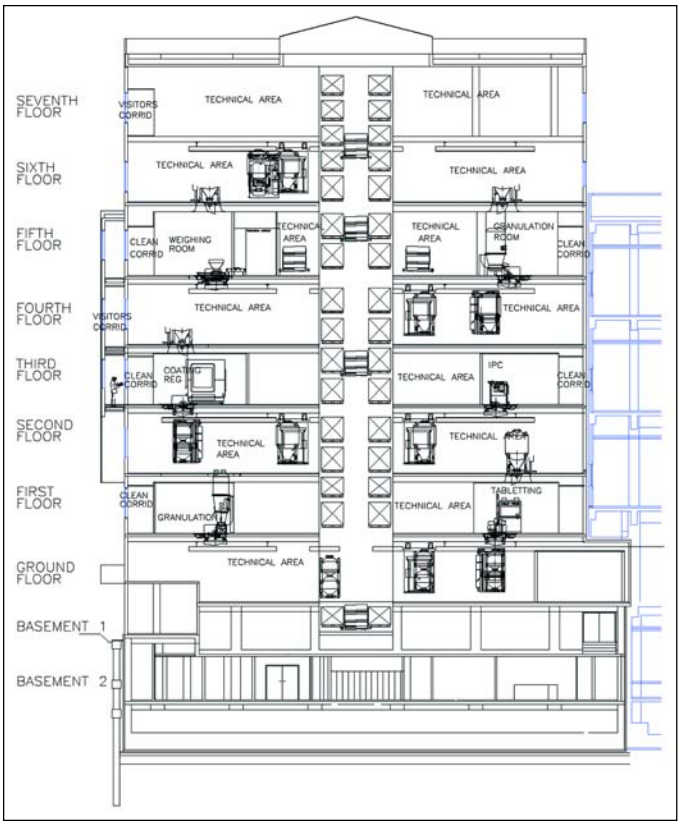

Figure 3. The Pliva plant in Zagreb, dedicated on December 12, 2001, is a center of excellence and one of the technically most advanced plants in the world today. It includes three production levels and four technical levels distributed around a central automated warehouse. Two additional levels in the basement are devoted to changing rooms and main sources of energy.

These concepts, currently called the "Lhoest Concepts" or "Lhoest type plants" are widely spread in the industry.[2,3,5,6] It is estimated that more than 200 plants around the world are now using them in part or in totality.

The Pharmachemie plant constructed in 1990 in Haarlem, The Netherlands (Figure 2), the Roche plant built at Segrate, Milan, Italy in 1999, the KRKA plant at Novo Mesto (Slovenia) completed in 2000, and the most recent Pliva plant in Zagreb (Croatia) (Figure 3), are typical examples of the concepts under consideration.

All of these advanced facilities share the following basic characteristics:

- storage of products in technical areas, above and/or below the production floor at all stages of manufacturing
- drastic reduction in size of cleanrooms and HVAC requirements
- gravity flow of products
- closed systems, based on the bin technology
- multi-level constructions
- islands of automation
- automated materials handling
- fully automated warehouses
- computer integration

Table A compares the main characteristics of modern automated plants with conventional technology.

Potential Savings and Justified Concerns

It is true to say that important savings, originating mainly in a drastic reduction in the size of cleanrooms, can be achieved in the construction of tabletting plants or Oral Solid Dosage Forms (OSD) plants. This is done by keeping the powder, granule, tablet, and capsule containers, ie, Intermediate Bulk Containers (IBCs) or Bins, and consequently all the material handling outside the clean areas, as well during process, storage, and transportation.

Important savings can be achieved by keeping the IBCs and the Material Handling Systems outside the clean production areas.

However, it appears that several pharmaceutical companies who constructed new OSD facilities in the past 15 years decided, in spite of these important potential savings, to select the most expensive solution and to locate their IBCs and consequently the whole material handling system - automated or not - inside the clean areas.

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The reasons that explain these non-economical decisions are:

1. a lack of confidence in the quality of the separation between the clean production areas and the technical zones, and more specifically, a lack of confidence in the docking stations since they represent the most critical interface between the products stored in bins, in technical areas, and the process machines located in the cleanrooms

2. an even greater lack of confidence if the products to be handled belong to the categories of highly active products: steroids, hormones, cytostatic products, or allergenic compounds such as lactame products, penicillins, etc.

3. justified concerns about the cleaning of some docking stations and some connecting ducts that, until now, have to be performed from the technical side with all the risks linked to the dismantling of dusty parts in non-contained areas

4. similar justified concerns about maintenance that cannot always guarantee a total absence of powder dispersion

A. Types of Docking Stations

In a regular OSD automated plant, several types of docking stations are needed. It is important when evaluating a system to look not only at the feeding station which is often the current model proposed, but at all models of stations including complex ones like the weighing stations.

Currently for OSD plants, the following types of stations may be needed:

1. Feeding Stations - these stations allow discharging an IBC by gravity through its lower valve from an upper technical level into a process machine located in a cleanroom.

2. Receiving Stations - they accomplish the reverse. They allow collecting the product elaborated by a process machine in a cleanroom into an IBC located in the technical area below.

3. Weighing Stations - these are the most complex ones. Basically they derive from receiving stations, but in addition they incorporate several scales. They are able to weigh and dispense raw materials from a cleanroom into a bin located in the technical area below. They must ensure a perfectly tight connection between the clean weighing room and the technical area which both operate at different air pressures without influencing the accuracy of the weighing operation.

4. Feeding Stations for Tablets - since tablets, coated tablets, and capsules are more delicate than powders, they require different types of valves, different conduits, smoother slopes, and devices to prevent them from dropping from an unacceptable height, etc. The complete design must ensure that no tablet can be damaged during filling, storage, or transfer, and also that no tablet can remain trapped in the system with the risk of being introduced in another batch. Feeding stations for tablets are used essentially on top of coating pans, packaging machines,

	CONVENTIONAL PLANTS	MODERN PLANTS
1. Construction	Mono-level Buildings	Multi-level buildings
2. Product transfer	Lifted at every process step	Gravity from floor to floor Vacuum exceptionally
3. Type of containers	Large variety Non standardized	Standardized and custom designed SS containers
4. Transportation	Fork lifts. Pallet movers Manual	A.G.V.'s and transfer cars 100% Automated
5. Circulation corridors	Wide (3-4m) for fork lifts	Narrow. Only for personnel
6. Lay-out	Based on fixed sequence of process rooms	Based on flexible manufacturing systems (F.M.S.)
7. Operation	Manual	Computer guided
8. Air handling	Applied to total plant volume	Applied to only 1/5 to maximum 1/3 of the total plant volume
9. Product exposure	Exposed to ambient air	Kept in air-tight containers and closed transfer systems
10. Flexibility	Limited	Maximized
11. Circulations of: production operators, maintenance personnel, janitors, visitors,...	All circulations intermixed. Potential source of cross-contamination	All circulations fully segregated No risk of cross-contamination
12. Warehouses	Pallet racks served manually by forklift trucks	100% automated and computer guided
13. Maintenance	Inside production rooms	Basically from outside the production rooms
14. Quality control	Separate laboratory	On-line control, using a closed loop Higher automation
15. Batch records	Paper documents	Electronic supports
16. Automation	Linked to mass production Based on continuous flow Mainly electro-mechanical Computer monitored	Possible also with small batches Computer guided production and Q.A. with on-line liaison to management computers

Table A. Sixteen main differences between conventional plants and modern concepts.

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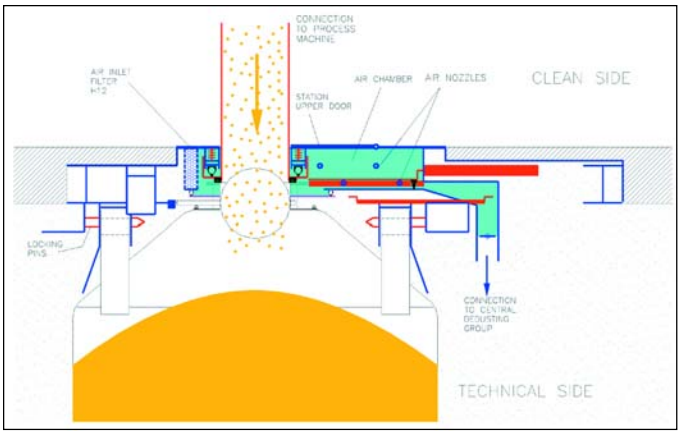

Figure 4. A typical receiving station of the 5th generation with the suspended bin.

and inspection equipment, etc. Tablets can be stored in bins in quantities of several hundreds of kg and even up to one ton.

5. Receiving Stations for Tablets - the same comments apply to receiving stations for tablets as they leave the tabletting, coating, printing, or inspection rooms.

6. Drying Stations - they are less frequently demanded, but they are used in some plants for the final drying of coated tablets, mainly sugar coated tablets, stored in bins after the regular coating process. This allows a shorter coating time, reduced handling of such tablets, and an increased output of the coating equipment.

7. Parking Stations - these are storage positions for IBCs. They are very simple and require only a good positioning system.

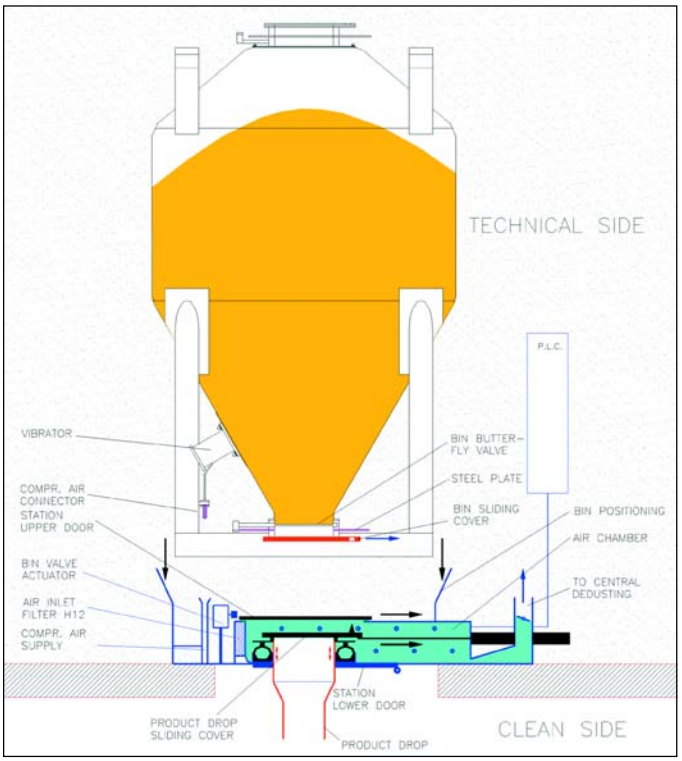

Figure 5. Feeding Station - Overall View. The feeding station is essentially a tight air box with an upper and a lower door of which only one can be opened at a time. It is maintained permanently under a slight negative pressure and under a flow of HEPA filtered (H12) air. It is self-cleaning.

Depending on the selected concept they may include an indication of the presence of a bin, and if wanted, some communication system with the plant computer.

B. IBCs/Bins

At first sight, IBCs or bins look like very simple stainless steel containers. However, the selection of an appropriate bin is a very important decision in a renovation or in the study of a new plant. Its importance is very frequently underestimated.

The most current ones are the powder bins, the tablet bins and less frequently, the liquid bins used for coating and granulation solutions.

One of their most important characteristics is that bins must be adjusted to the economical batch size or batch sizes to be used in the new plant and the determination of this economical batch size is a complex equation.

The flow characteristics of the products also have to be taken into account.

Specially designed tablet bins are able to accommodate up to one ton of bulk tablets, coated tablets, or capsules, but very often require some adaptations to the specific products.

In addition, IBCs must obviously be adapted to the type of stations selected since their upper and lower valves, compressed air connections, seals, and commands must perfectly match with the corresponding stations.

They must be adapted to the selected material handling system (AGV, Elvecar, shuttles, conveyors). This applies not only to the mechanical adaptation of both units, but also to the electronic communication system for bin and product identification, batch recording, and product tracing.

Finally, they must be adapted to the tumbler blender and to the automatic washing bin.

Overall, the selection of the bin type, shape, and size is one of the most important decisions to be made in the process of studying a new production facility.

Bins require a specific study as do all stations including the tumbler-blender, automated washing(s), and the material handling vehicles. This must be a global study, perfectly coordinated, to be carried out by specialists experienced in production planning and process optimization.

Bins must be adjusted to the economical batch size. If possible, each bin should correspond to one full batch. Different and interchangeable bin sizes are frequently used in automated plants.

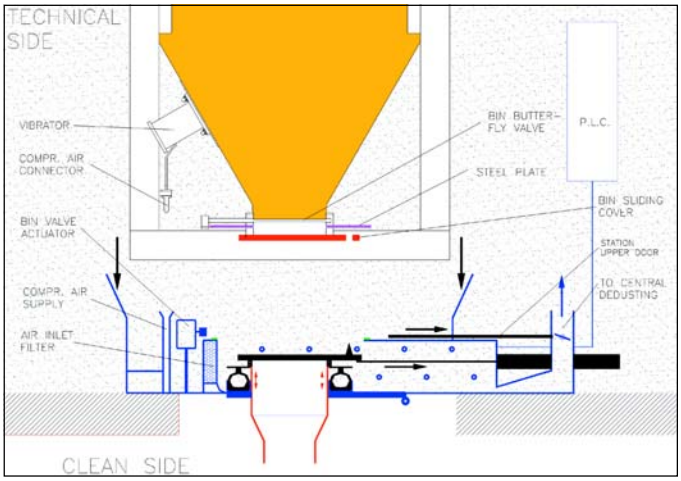

Figure 6. Step 1: The bin comes down vertically and the station upper door slides open.

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> ***Bins require a specific study as do all stations...***
> ***<u>This must be a global study</u>, perfectly coordinated, to be carried out by specialists experienced in production planning and process optimization.***

C. Weaknesses in the Field of Docking Stations

Since the construction of the first feeding stations in 1982, many machine manufacturers or stainless steel equipment producers developed their own systems and invaded this completely new market. However, some of these systems revealed weaknesses that did not allow the industry to fully benefit from the significant savings linked to the use of the concepts under discussion. For similar reasons, they did not completely penetrate the market, especially the area of dangerous or highly active drugs.

These weaknesses relate to one or several of the following fields:

- Tightness
- Active Dust Dispersion
- Maintenance Issues
- Leakage from the Cleanrooms
- Validation Issues

- **Tightness.** Some stations are not always perfectly tight and allow active product to leak through seals, valves, or the junction between the bin and the station itself.

- **Active Dust Dispersion.** Most docking stations must be dismantled in the technical area in view of their cleaning. The dismantling and the handling of station dusty components may cause a release of active dust in the technical area. Also, it is almost impossible for the operators in charge of dismantling to avoid direct contact with active dust or spreading of contamination in areas not designed to contain it.

- **Maintenance Issues.** Similar concerns are expressed with respect to maintenance operators when they have to repair or maintain the stations from the technical side. Depending on the type of problem, it is not always possible to clean the station before allowing maintenance to proceed.

- **Leakage from the Cleanrooms.** Other concerns originate from the fact that during some phases of cleaning, dismantling, or maintenance, a direct connection is created - even for a short time - between the technical area and the clean production room that usually is at a higher air pressure and therefore is able to blow active dust in the technical environment.

- **Validation Issues.** Some systems are not validatable because they fail to comply with the aspects of tightness or active dust dispersion described. Other ones are not re-validatable because they fail to keep their properties with time or in front of the difficult challenge of perfectly matching all bins with all stations in a plant.

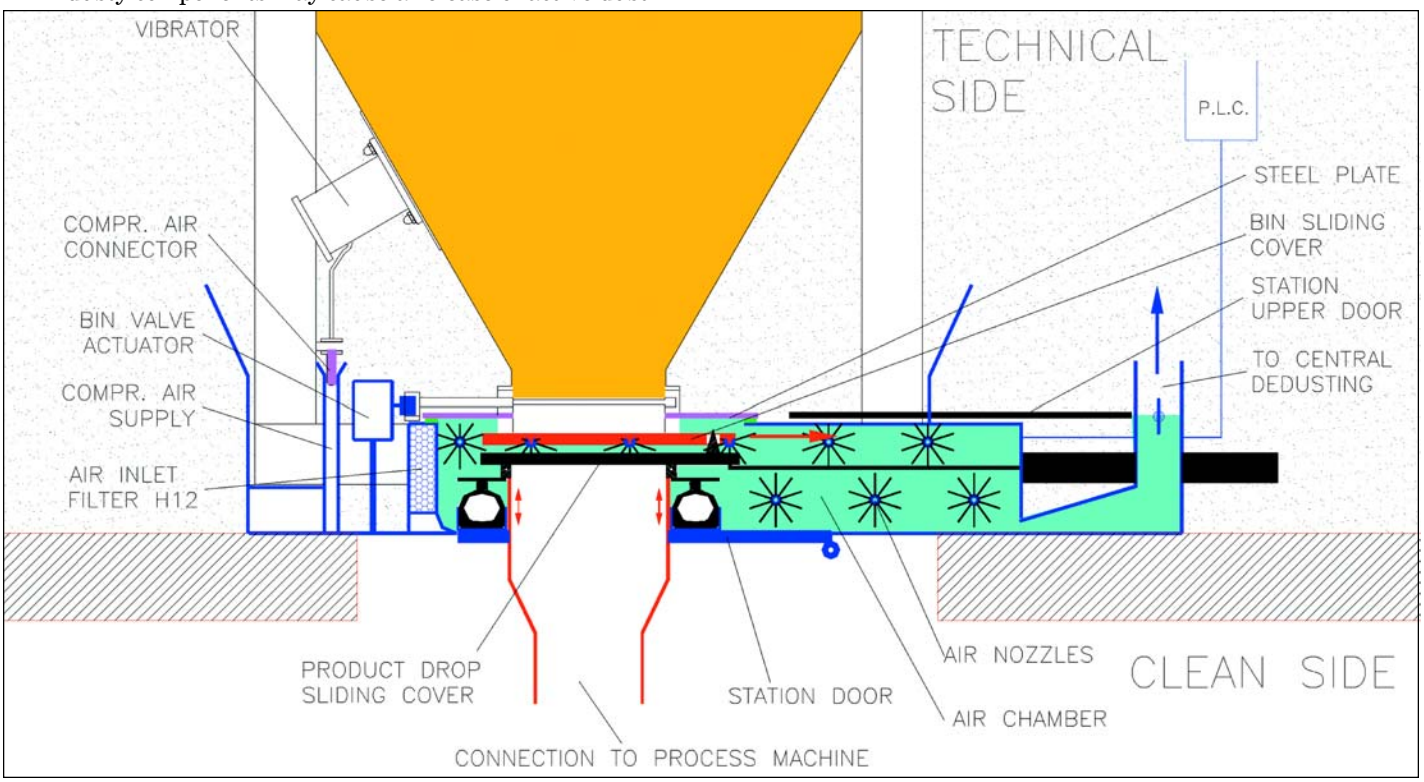

Figure 7. Step 2: As soon as the bin is docked, the air chamber is flushed by jets of medical grade compressed air. After flushing, it remains under a slight negative pressure and under a gentle flow of HEPA (H 12) filtered air.

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> ***The first stations built in the 1980s were rather primitive and would no longer be accepted today. Multiple improvements were made during these 20 years.***

The first stations built in the 1980s were rather primitive and would no longer be accepted today. Multiple improvements were made during these 20 years. Progress was made stepwise and we are now at the fifth generation of Docking Stations for pharmaceutical use.

D. The 12 Requirements for Good Docking Stations

Under today's cGMP and legal requirements, the main criteria defining good docking stations for use in modern tabletting or OSD plants can be summarized as follows:

1.Tightness

Good docking stations should ensure a perfectly tight separation, at all times, between technical and clean areas, even under different air pressures.

They should guarantee the absence of any air exchange and of any particle movements between technical and clean areas, at any time, and especially during cleaning inspection or maintenance phases.

This tightness should be validated on the basis of DOP tests, smoke tests, swab tests, or equivalent.

Good docking stations must guarantee a tight separation between clean production rooms and technical areas at all times, and more specifically during docking, transfer of powders, cleaning, maintenance, and inspection phases.

2. Air Lock Function

This required tightness could be achieved by applying the well-established principle of the air lock.

As any air lock, it would be opened as wanted, either from the clean side or from the technical side, but only one side at time. As any good air lock, it could be swept intensively by clean air, and even, if wanted, by sterilizing gases. Ideally, it would be kept at a different pressure - usually a lower pressure - than any adjacent room.

3. Direct and Easy Access from Both Sides

A direct and easy access to the interior of the station should be possible:

a. from the technical side - for inspection and maintenance
b. from the clean side - for inspection and cleaning

Whatever side is opened, the tightness of the separation between clean and technical areas should be guaranteed at any moment.

4. Short Connections

Dismantling of a conduit in a technical area is always a potential source of cross-contamination and should be avoided.

Long connections with bins are sources of additional costs, increased product losses, and certainly increased difficulties in dismantling, cleaning, drying, and reassembling operations.

Therefore, the station should allow the shortest possible connection with the process equipment. Ideally, no section of tubing should appear in the technical area, and no piece of the

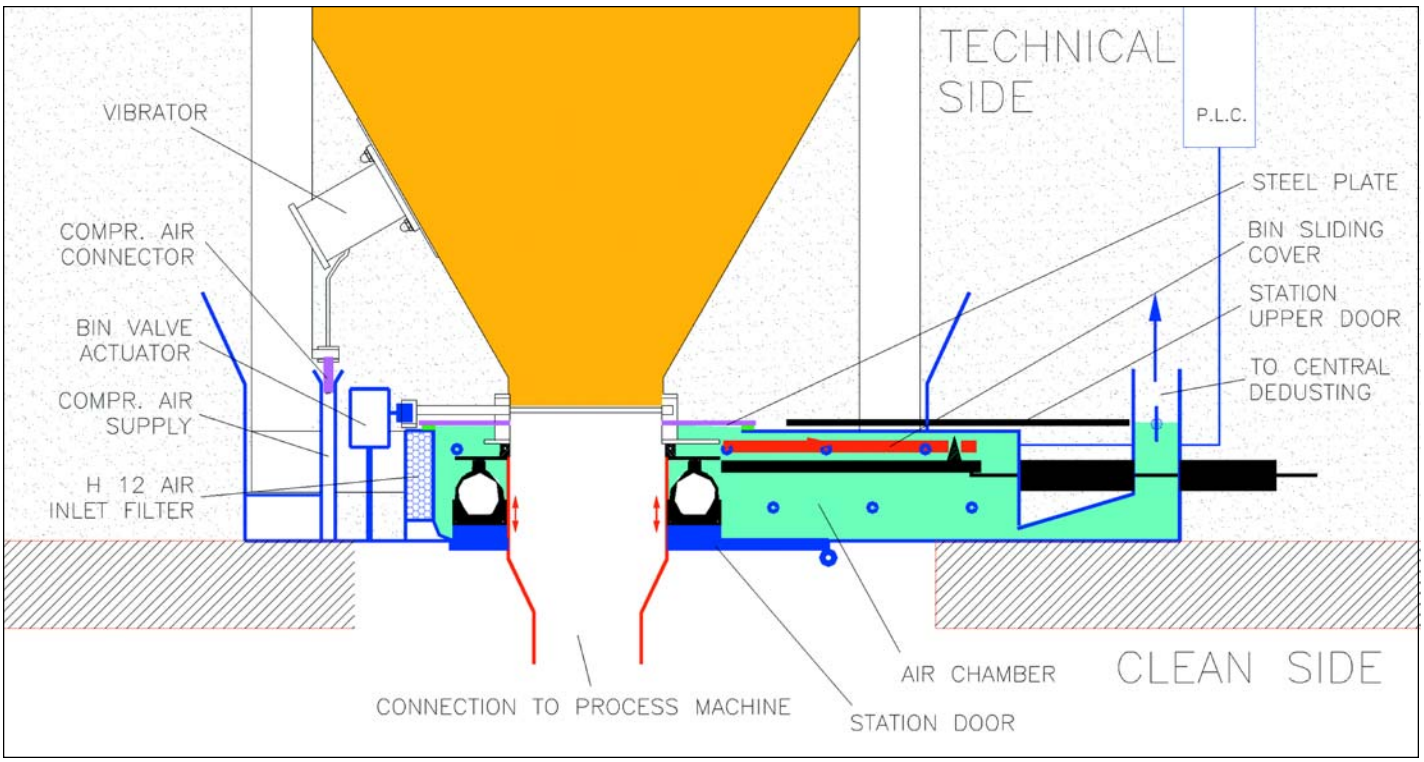

Figure 8. Step 3: Both sliding covers open horizontally and the powder drop is pressed against the bin flange. The docking operation is completed.

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station should be disassembled from the technical side before cleaning.

Additionally, long vertical connections between bins and production equipment lead to higher ceilings in the construction and to unnecessary additional costs.

This leads to a concept of stations where the active parts are either located on the slab or incorporated directly in the slab thickness as shown in Figure 4.

5. Ease of Cleaning

Most attempts at fitting docking stations with clean in place systems failed because of the added complexity and mainly because of the significant additional time needed for the washing and drying operations. Many users also are reluctant to accept risks of potential dripping above the process machines.

The ideal station should not require any wet cleaning.

6. Robustness and Simplicity of Construction

It is of primary importance to ensure that the whole concept, including docking elements, authorizes a construction with generous tolerances, several mm, and guarantee robust and durable low maintenance operations.

It is difficult and therefore costly to construct a series of containers up to 2000 or 3000 liters in capacity, that always fit within a few tenths of a mm to any station in the group. It is an even bigger challenge to guarantee that wear and tear or some distortions during 10-15 years of daily service will allow to maintain such tight tolerances, especially around the valves and their docking surroundings.

7. Very Flat Construction

Feeding stations are one of the determining elements for the ceiling height in technical areas. Consequently, they also influence the total height of the building itself. A station with a frame height of 50 cm or more no longer appears attractive from this standpoint since it greatly impacts the height of the building. Furthermore, this cost penalization is often repeated for every technical floor of the building.

For the same reasons as outlined in Figure 4, no connecting tubes should appear in the technical areas. Receiving stations should be incorporated in the slab thickness.

8. Vertical Bin Movement

In the past years, two different approaches have been used for bringing bins to their stations.

The horizontal approach whereby the bin moves on roller conveyors and connects to the station through a horizontal translation.

The vertical approach whereby on a feeding station, the bin is put down vertically by the transport vehicle, or whereby on a receiving station, the bin is lifted vertically against the station and clamped to it. Lifting tables and lifting columns also are used in similar situations.

Vertical docking is preferable for the following reasons:

- It saves floor space: a vertical station uses in general less than 50% of the floor area required for a horizontal one with its entrance conveyor.
- It eliminates the roller tables or horizontal conveyors and their drive (s) which represent additional cost, more complexity, additional maintenance, and cleaning issues
- It allows to incorporate the station, partly or totally, in the slab thickness and thereby to shorten the bin connection duct.

9. GMP Construction

All parts in contact with the product should be either SS 316, polished at R_A of 0.8, or better. Elastomers should be food grade or FDA accepted. All angles should be smooth, surfaces should be devoid of any cracks, slits, or recess area of any type.

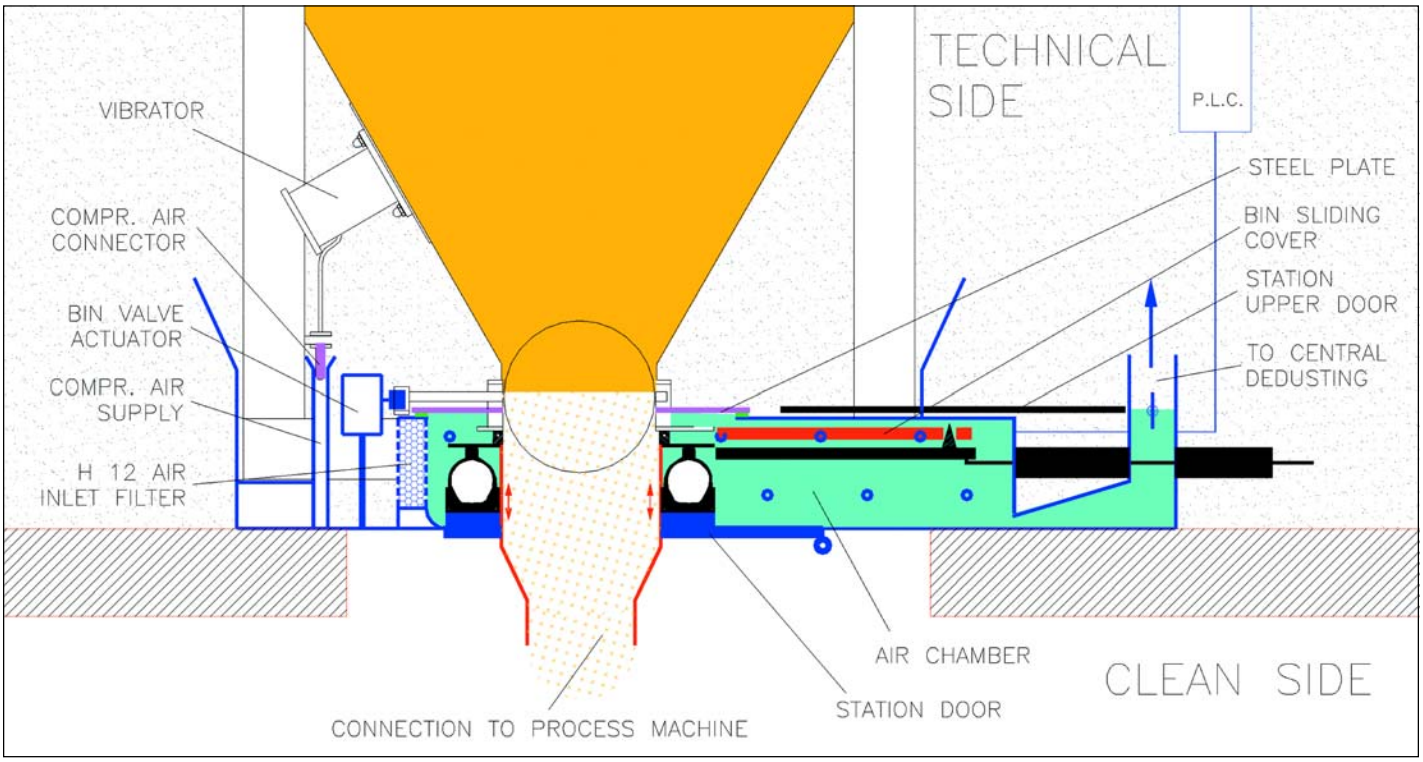

Figure 9. Release of the Product. On command by the operator in the cleanroom, the butterfly valve opens gently and releases the product to the process machine.

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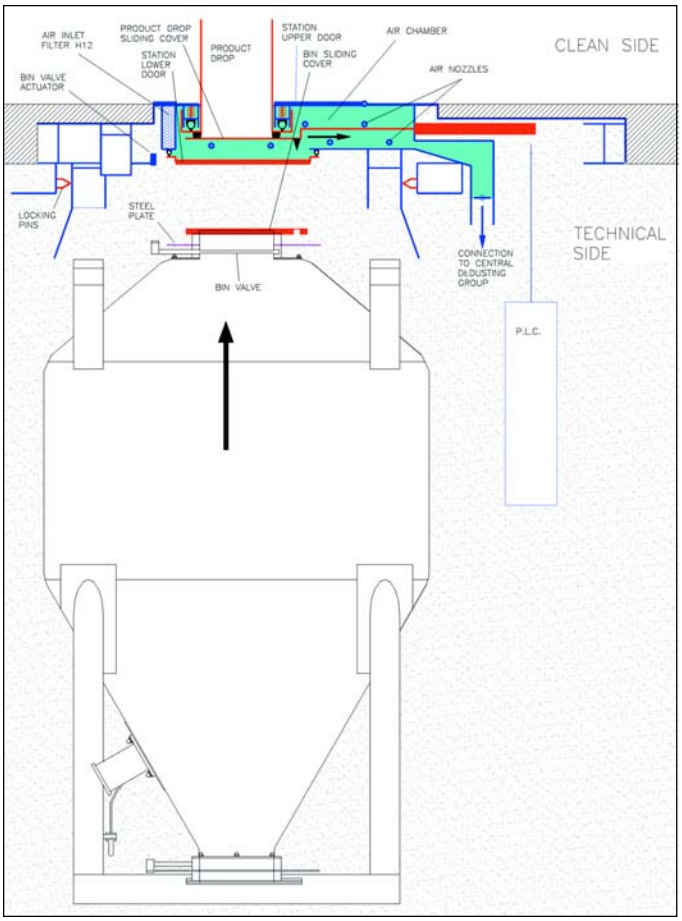

Figure 10. Receiving Station - Overall View. The receiving station is almost identical to a feeding station that would be turned upside down. The main differences:
A. The station is embedded flush with the floor of the cleanroom.
B. After lifting against the station, the bin remains suspended from the station by means of 4 automatic locking pins. This enables to get a very short connection with the bin, to look into it and to take samples from the cleanroom.

If air is used in the station chamber, it should be HEPA filtered. Compressed air coming directly or indirectly in contact with the product should be medical grade.

10. Flexibility

The system should be able to handle tablets as well as powders, granules, pellets, hard gelatin capsules, etc. It should be easily adapted to the weighing process.

Well thought standardization, use of easily found components, and design of elements common to several types of stations should be encouraged.

11. Easy Dismantling and Maintenance

All parts requiring cleaning or inspection should be made easy to dismantle, by one single person, from the clean side, and without tools. Ideally no lubrication should be needed.

Maintenance should be performed entirely from the technical side after due cleaning from the clean side, if required.

12. Price Acceptable and Justified

The price should remain reasonable and justified.

Currently, the experience shows that the savings produced by the modern plant concepts compensate the cost of excellent docking stations and of the automated material handling. This allows a modern automated plant to be constructed at the same cost as a conventional one of the same capacity. On the other hand, it produces very high savings in direct operating costs.

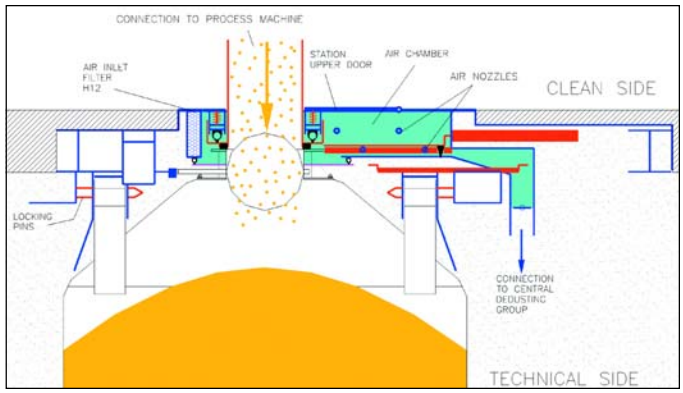

Figure 11. The bin docked to the receiving station with its upper valve open. As with the feeding station the three docking steps are: 1. the opening of the station door and connection of the bin; 2. the complete flushing of the air chamber and junction pieces by jets of medical grade compressed air; and 3. the opening of the sliding covers while the air chamber remains permanently under a slight negative pressure and a flow of HEPA (H12) filtered air. Release of the Product: The start-up of the process is commanded by the operator in the cleanroom, the butterfly valve opens gently, and the product can be released from the process machine.

E. Description of the Fifth Generation of Docking Stations

The new, patented docking stations of the 5th generation[8] combine most of the criteria requested.

They can be described as an airlock equipped with two doors, properly interlocked so that only one can open at a time, and a flow of HEPA filtered air, reinforced by strategically located air jets, ensure a self cleaning effect, and a very high number of air exchanges. The recovery time is less than three minutes.

One of the here-above doors enables the bin to dock with the station, while the opposite door gives access to the clean production room.

Additionally, a series of mechanisms allow to dock or to undock the bin, in a manual or in a full automatic mode, in absence of operators at any time of the day or night, weekends included.

The docking operation, whether it is a feeding, receiving, or weighing station, can be divided into three steps:

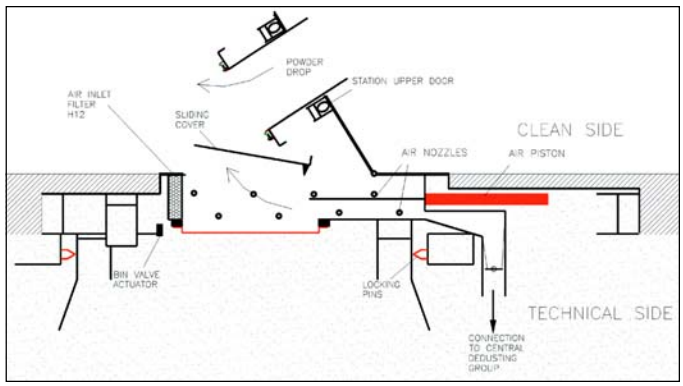

Figure 12. Cleaning, Dismantling, and Inspection of the Station. For all stations of the 5th generation, a door which opens in the cleanroom gives direct access to the air chamber. As said before, it is self cleaning and does not come in contact with the flow of product. The only component entering in direct contact with the product is the powder drop and to a minor extent the sliding cover. Both elements can be removed in seconds from the cleanroom side and washed with water as required. Alternatively they can be readily exchanged with clean ones.

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1. the bin approaches and docks with the station in a smooth vertical movement

2. the station airlock that encloses all docking elements is flushed by jets of medical grade compressed air (sterile if wanted)

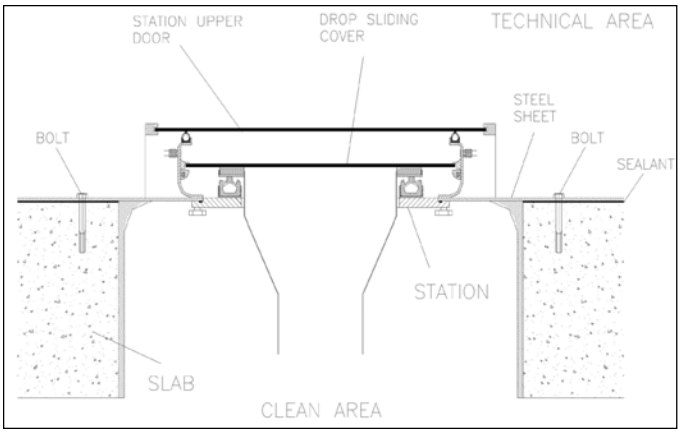

Figure 13. Station in Stand-By. Double barrier protection between clean area and technical area.

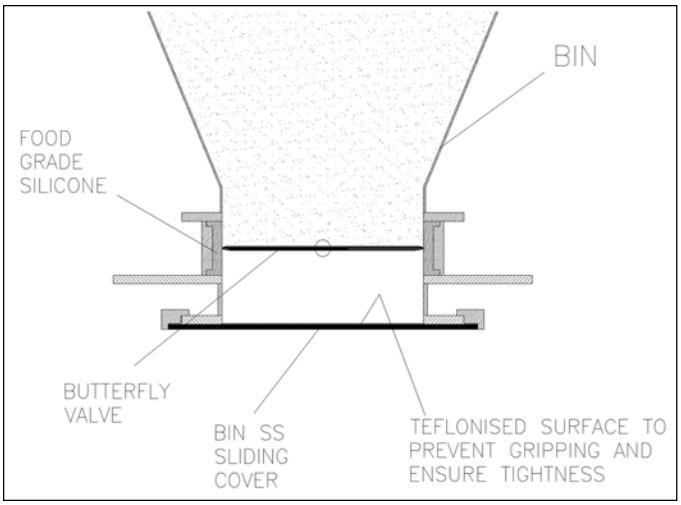

Figure 14. Double barrier protection (butterfly valve and sliding cover) to keep the bin tight. The same protections apply of course to the upper opening of the bin.

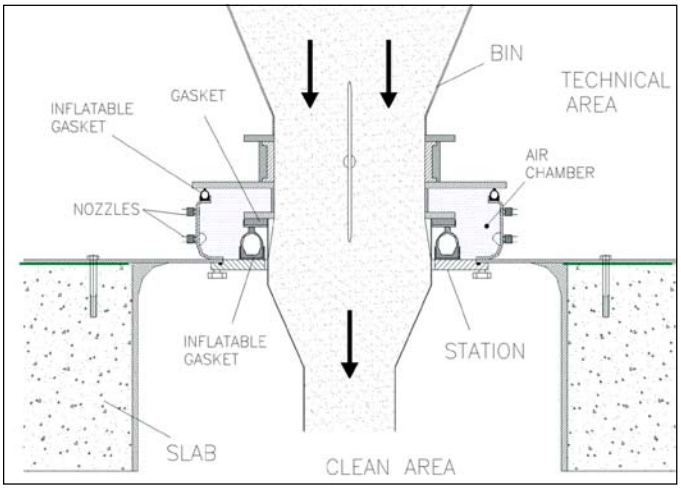

Figure 15. Situation during product transfer. Double protection of the product by the bin walls and conduits and by the air chamber surrounding the junction point.

3. the docking elements are connected together, automatically, and under perfectly clean air atmosphere. The air chamber of the station remains permanently under a slight negative pressure and under a smooth flow of HEPA filtered air. These operations are illustrated in Figures 5-9.

In the undocking operation, exactly the same sequence takes place in the reverse order.

1. After closing of the bin valve by the operator, the station air lock and connecting elements are automatically flushed by jets of medical grade compressed air.

2. The docking elements are separated automatically in a perfectly clean and dust-free atmosphere.

3. The bin is removed vertically by the transport vehicle and the air chamber is closed again.

These operations are illustrated in Figures 10-12.

F. Advantages of the 5th Generation Docking Stations

The new, patented stations satisfy all main requirements demanded by state-of-the-art docking operations. Their unique advantages derive essentially from the conditions created by the concept of the surrounding chamber maintained under a negative pressure.

1. A full separation between the clean process area and the technical area **at all times,** whether it is during storage, docking, transfer, production, undocking, cleaning, inspection, or maintenance phases.

2. A reinforced tightness due to the fact that:

   - all critical docking elements are separated from the room environment by a perfectly tight chamber and the docking operation itself takes place in this chamber
   - the chamber is permanently flushed by HEPA filtered (H12) air
   - the chamber is maintained permanently at a negative pressure with respect to adjacent rooms

3. At all times, whether the system is in stand-by or in operation, one can say that the product and the cleanroom are permanently protected by a double security:

   - station cover and drop sliding cover for the protection of the cleanroom (Figure 13)
   - bin valve and bin sliding cover for the bin itself (Figure 14)
   - closed conduit system and air chamber under slightly negative pressure during the process itself (Figure 15)

The stations of the new generation ensure perfect segregation, even with highly active products, between clean production rooms and the rest of the plant. The product is protected by a double barrier at all times and specifically during storage, docking, transfer, production, undocking, cleaning, inspection, or maintenance phases.

Figures 13-15 illustrate the here-above points.

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4. Short change over time. The new stations have the advantage that the air chamber is self-cleaning, which reduces down to four to five minutes the changeover time between different products.

5. The stations offer the possibility of operating in the presence of inert gazes such as Nitrogen or CO_2 if the process requires it.

6. They can be easily adapted for transfer of sterile products and for operation under fully sterile conditions.

7. The stations eliminate any possibility of cross contamination or transfer of dust between the clean production rooms and the technical areas.

Conclusions

In conclusion, it can be said that after 20 years of continuous improvement in the field of docking stations, the stage has now been reached where:

- the issue of transferring automatically and under perfect GMP conditions, products from bins located in technical areas into process rooms or vice-versa, is totally resolved by the 5th generation stations

- similarly, the transfer of highly actives or dangerous compounds is no longer an issue

- the transfer of sterile powders under similar conditions also can be envisaged optimistically with some additional precautions

The new generation of docking stations resolves critical problems that were identified with previous systems.

References

1. Lhoest, W., and Froment, P., "A New Design for Pharmaceutical Facilities. The Lhoest-Froment Concept," **Pharmaceutical Technology,** June 1984, pp. 28-40.
2. Cliff, M.J., "Tablet Facility Design for Flexible Production" European Pharmaceutical Review, June 1996, pp. 25-35.
3. Cole, Graham C., Pharmaceutical Production Facilities. Design and Applications. Ellis Horwood (1990) p 69.
4. Proceeding of the ISPE Seminar in Amsterdam, November 27-28, 1995.
5. Lhoest, W., and Ober, D., Glatt Symposium, 1994.
6. Schwind, G.F., "The Automated Factory. Computer Integrated Manufacturing, Italian style," **Material Handling Engineering,** May 1989, pp. 44-50.
7. Lhoest, W., and Vereeken, M., "Twelve Years Experience in Pharmaceutical Plant Automation." **Pharmaceutical Engineering,** March/April 1994. pp. 36-46.
8. USA patent 5,490,546 - European patent 0619254 - Other patents pending.

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About the Author

Willy J. Lhoest obtained his PhD in pharmacy from the University of Louvain in Belgium and a master's degree from the University of Wisconsin. He spent 29 years at SmithKline (now GlaxoSmithKline) where he held several positions in R&D engineering, and served 10 years as European Director of Manufacturing. He was responsible for the teaching of Pharmaceutical Technology and lectured as invited professor at several universities. In 1988, he became president and co-founder of the Company Elveco S.A. and specialized in Pharmaceutical Consulting, Engineering, and Validation. He is the author of more than 50 publications, 15 patents, and developed many new systems now in current use in our industry. He was named ISPE Engineer of the Year in 1987, and holds many other recognitions from the International Pharmaceutical Federation, the Baron 500, etc. He participated very actively in the introduction of ISPE in Europe by organizing the first ISPE Congress in Brussels. He now has more than 46 years of uninterrupted service to the pharmaceutical industry.

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This article discusses ways to reduce changeover time and increase line runtime. It focuses on packaging lines, but will apply generally to all other areas of manufacturing.

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How to Develop and Implement a Quick Changeover Program

by John R. Henry

Introduction

Any company involved in manufacturing is under constant pressure to reduce the price of the product. Previously, pharmaceuticals were somewhat immune to this pressure, but this is no longer so. The only way a company can survive, much less grow, is by constantly striving to reduce costs and increase productivity. Reduction of downtime from changeover is an important factor in increasing plant productivity.

Changeover is defined as the total process of converting a machine or line from one product to another. The product could be either completely different or could be the same product in a different size.

Changeover can be broken down into three components, called the "3 Ups." These are:

Clean-Up

Cleanup includes all actions taken to remove the previous product as well as all components and materials from the line. It may be very quick and simple as in the case of changing from an English to a French language label for the same product. It also can be very complex and time consuming as in the case of a parenterals line which must be completely disassembled, washed, and sterilized.

Set-Up

Set-up and changeover are sometimes used interchangeably, but this usage is incorrect. Set-up is a component of changeover, but only a component. Set-up is the process of adjusting or changing elements of a line to convert it from one product to another.

Start-Up

Start-up, sometimes called run-up or ramp-up, is the time consumed after clean-up and set-up are complete and the line is restarted in production but before it is running at normal speed and efficiency. It is characterized by machine jams, damaged and rejected product, spills, and perhaps most of all, by tweaking of the line by the mechanics to bring it into conformance and get it "settled down."

Documentation as well as the introduction of the new product and materials to the area also comprise part of changeover and can usually be included within one of the 3 Ups.

The proper goal with respect to clean-up and set-up is to reduce them. The only proper goal with respect to start-up is elimination. Start-up, with the exception of a new product run for the first time, is caused by variation. This variation can occur in the set-up process or it can occur in the product or materials.

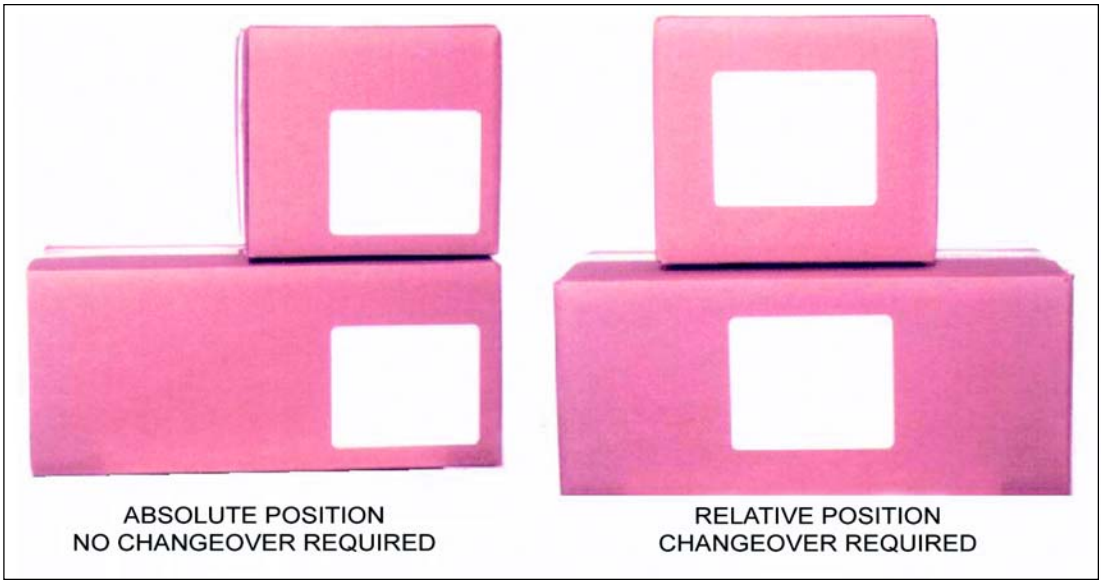

Figure 1. Absolute and relative label position.

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For any given product, there is going to be one combination of machine settings that gives optimum results. The goal must be to precisely achieve this combination of settings during the set-up. The unacceptable alternative is to approximate the settings then fine tune them after the line has restarted. Elimination of all variation in set-up is critical.

The second source of variability is in the product or components. If a syrup is being filled, it may be that the settings of the filler can be reestablished precisely time after time. If the viscosity of the syrup varies from lot to lot, perhaps due to temperature changes, it will not matter how precisely the filler is set up, the settings will be different every time to compensate for the varying product.

A good changeover program will directly address the first type of variability. It will develop SOPs that describe exactly how the machine is to be set up. It will modify the machine if necessary to assure that measurable and repeatable quantitative settings are possible. And, it will train the set-up people to perform the changeover correctly.

A changeover program will indirectly address the issue of product variability. If it can be demonstrated that there is no variability in the set-up, it will be possible to show that the variability causing start-up is occurring in the product. It also will be possible to determine the costs associated with the variability. This will put pressure on the purchasing and/or manufacturing departments to reduce variability.

The definition of changeover time can be derived from the above. Changeover time is the total elapsed time from the last unit of good production of the previous run at full line efficiency to the first unit of good production of the succeeding run at full line efficiency. In some cases, a line will be slowed down as the production run ends. Additionally, there will be a period of less than normal efficiency called start-up. Both of these periods must be included in the measurement of changeover time.

It is important to note that changeover time is an elapsed time rather than labor hours. While it is always desirable to reduce labor hours where possible, the cost of labor is usually low compared to the cost of downtime. The primary goal must be to get the line back up and running in the shortest amount of time possible. Reducing total labor hours involved should be a secondary goal. Of course, as they say, "your mileage may vary" and this statement, while generally true, must always be justified.

Preparing for the Program

The first question to be asked when considering a changeover program is why it is being done. Of course it is being done to reduce costs, but there are several factors to this. A changeover program can reduce inventory (raw material, in-process, and finished goods) levels by allowing smaller batch sizes. It can increase plant capacity by increasing the amount of time the plant is running. It can be used as a marketing tool to provide quicker response to customer requirements. It could be implemented to gain better use of available personnel. It is important that the reasons for the program be defined, as this will influence its implementation.

As the reasons are defined, the expectations for the program should be defined as well. It is often hard to precisely define the expectations prior to implementing the program, but an attempt should be made to establish them at least in broad general terms. This will help prevent unrealistic expectations. Unrealistic expectations are always a foundation for disaster as management finds that the expected results are not there and the team members find that they cannot meet the goals. Demotivation sets in, the program dies painful death and for years afterwards people say, when asked about changeover, that they tried it and it doesn't work. It is better to have no program at all than one doomed to failure.

Management must demonstrate full commitment to the program. People, in general, will do what they feel their superiors think is important. If management is not committed to changeover reduction as a high priority, it will not be a priority for anyone else as well. Management must be prepared to provide both moral support and physical support in the form of required resources. Naturally, any resources must be justified and even when fully justified may still not be forthcoming. In this case, management owes at the very least an explanation of why they are not available.

One important resource that must be forthcoming is training for the team. They need to be taught how to analyze changeover, they need to have access to books, magazines, videos, and other materials dealing with changeover. They also should have access to other plants within the industry and outside the industry to see what others are doing.

The number one key to a successful changeover program is management commitment. If management is committed and makes changeover time reduction a priority, it is almost impossible to fail. Without management support, it is almost impossible to succeed.

Another factor that needs to be considered is the length of the program. It is all well and good to say that this will be an open-ended program of continuous improvement. The problem is that everyone has seen continuous improvement programs under a variety of names come and go. The pattern is that they get introduced with a bang then peter out until the next big program is implemented. One way to get around this problem is to treat changeover reduction as a project or campaign. That is, it will have specific goals, a specific completion date (perhaps one year), budget etc. At the end of the period, the results will be evaluated, the people involved recognized, and the program comes to an end to be replaced with another changeover campaign. The people involved could be the same or different as could the goals. A series of campaigns will have the same effect as a continuous, open-ended process, but may make it easier to keep the enthusiasm.

Choosing the Team

It should go without saying that the composition of the team is critical to its success. Serious thought needs to be given to selecting team members. There are several qualifications to consider including knowledge, interest, ability to work with others, and perhaps most important of all, enthusiasm. The team should not include anyone who was "sent," all members should be volunteers.

In days of old, armies would conserve their strengths by selecting a champion. The story of David and Goliath is one such example. The changeover team needs a champion as well. The champion needs to be someone who truly believes. In fact, you might say they need to be a little bit nuts on the subject. They need to be able to convey this belief and enthusiasm and get other people charged up as well. The champion does not necessarily need to hold an official post of leadership on the team though it may help. The champion also does not necessarily need to be a manager or even a supervisor. The main qualification is going to be an ability to inspire and convince others that changeover reduction is the right thing to do.

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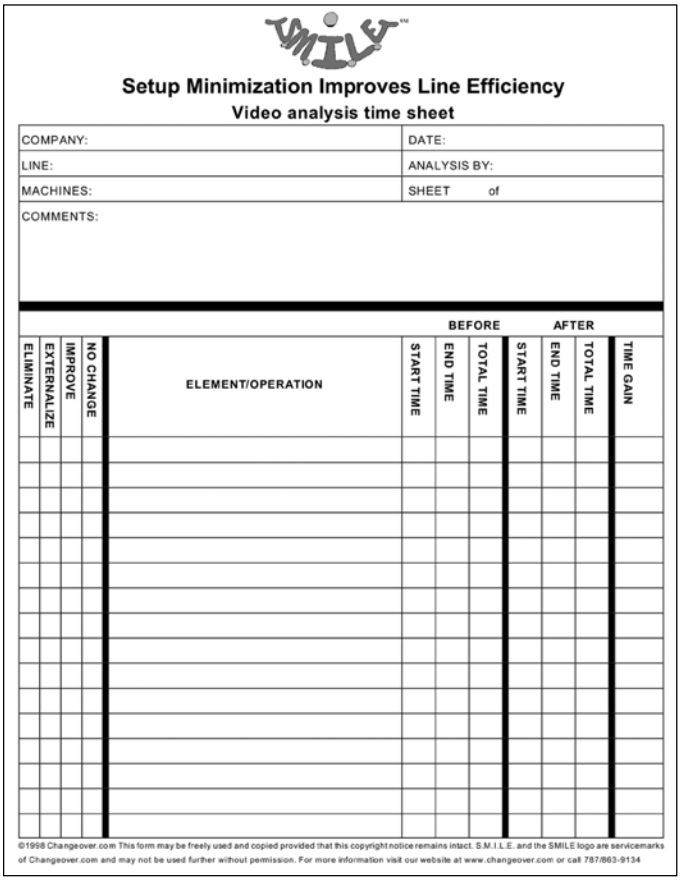
> ***The number one key to a successful changeover program is management commitment. If management is committed and makes changeover time reduction a priority, it is almost impossible to fail. Without management support, it is almost impossible to succeed.***

The other team members will fall into two categories: regular and ad hoc.

Regular members are those who are expected to attend meetings regularly. They will generally be the people directly involved with changeover. Typically, these members will include line mechanics, set-up technicians, operators, production supervisors, and engineers. In other words, regular members are the people who are working with changeover on a daily basis, who will be expected to implement the improvements, and who will receive the benefits.

Modifications to changeover processes will often have an effect on quality and it may be a good idea to have a representative from the quality team in regular attendance. Quality will often have a direct impact on changeover as they have responsibilities for documentation. If the changeover itself is reduced to from an hour and a half to thirty minutes and quality is still taking an hour to provide a line clearance, the team's work has been for naught. A quality representative on the team can help address both of these issues.

A representative from the validation department can be a valuable asset for similar reasons.



Setup Minimization Improves Line Efficiency

Video analysis time sheet

COMPANY:	DATE:
LINE:	ANALYSIS BY:
MACHINES:	SHEET of
COMMENTS:	

					BEFORE			AFTER			
ELIMINATE	EXTERNALIZE	IMPROVE	NO CHANGE	ELEMENT/OPERATION	START TIME	END TIME	TOTAL TIME	START TIME	END TIME	TOTAL TIME	TIME GAIN

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Figure 2. Video Analysis Time Sheet.

The responsibility for changeover is not limited to the people mentioned above. Every department in the company has a role to play and should be asked to designate a representative to the team. This representative need not normally attend meetings, but might be asked to do so when a matter involving their department is on the agenda. They also would be available to provide assistance in their particular area as needed by the team.

Some examples of different departments and their functions include:

Finance - As mentioned above, any project needs to be cost justified and changeover is no different. Many people can do financial justifications, but may need help when they get complex. Additionally, justifications that carry the finance department's "Seal of Approval" may carry more credibility.

Human Resources - Changeover reduction ideas may involve modifications to working hours and job descriptions. If this is the case, HR must be involved. When training is required, this also may fall into the HR bailiwick. Finally, HR will generally have responsibility for safety issues and will need to assure that all planned changes do nothing to endanger safety. Plants with labor unions must involve them as well.

Manufacturing - Manufacturing needs to understand the problems that variability causes and work to reduce it.

Materials - A line cannot start until all materials, components, and products are present. Lack of materials is a common bottleneck in changeover and the materials department will be responsible for its elimination.

Package Engineering - This may be a function of marketing or may be separate. The design of the package is a key function from the customer's point of view, but there will sometimes be changes that can be made with little or no market effect, but significant effect on changeover. An example is placement of labels on shipper cases - *Figure 1*. If the label is placed in the center of the shipper, each time the shipper size changes a complete adjustment to the labeler must be made. If, on the other hand, they can be placed in a constant position regardless of size, say 1" in and 1" up from the lower leading corner, the labeler changeover can be eliminated. Other possibilities include standardizing bottle footprints, reducing the number of shipper sizes, and the like.

Purchasing - Variability in components will cause problems in getting the line to run correctly after changeover. The purchasing department needs to understand the problems that can arise by using multiple vendors, vendors with

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Figure 3. Change part storage cart.

multiple plants, or simply vendors who cannot hold tolerances.

Scheduling Department - Production schedules can have a tremendous impact on changeover. If a plant is running three products in two bottle sizes, like bottle sizes can be scheduled together to minimize the amount of changeover.

The above list is meant to be illustrative rather than comprehensive. Different companies will have different requirements. The key to bear in mind is that everyone has a role to play in changeover and the team needs representation or access to all of them. The list is also in alphabetical order rather than order of importance.

Establishing the Ground Rules

In order to be successful, the team must be formally established and this means formal ground rules for operation. These rules will vary from company to company depending on local situations, but some of the more basic ones are:

Agenda - Every meeting must have an agenda. This agenda should include a review of old business, a report on progress, and completion of assignments from previous meetings by each team member and a list of items to be discussed. The agenda should be published in advance of each meeting to assure that each member can come prepared.

Assignments - During the course of meetings, members will be given assignments to complete. Once these assignments are accepted, the member is responsible for completing them on schedule. It is true that there will be cases where an assignment cannot be completed for reasons beyond the member's control and this is acceptable though the team should then do what it can to help with completion. What is not acceptable is that a member just not do an assignment.

Interruptions - During the meeting, no member should be disturbed for anything less serious than an earthquake.

Leader - Each meeting needs to have a leader or facilitator. This can be a rotating position to give each person a turn, it can be a permanent position elected by the team members or it can be someone appointed by management. The key is someone needs to be in charge to keep the meeting on track and prevent it from breaking down into aimless conversation.

Meeting Time and Place - A routine needs to be established so that meetings take place at the same time, day, and location. Ideally, a room should be set aside for the changeover team which would allow them to leave work in progress rather than need to get set up anew every meeting.

Minutes - A person needs to be designated as meeting recorder to take notes. This person will be responsible for publishing the minutes to all team members promptly (ideally within 48 hours) after each meeting. The recorder also shall be responsible for maintaining archives of all files related to the team's activities.

Process

Once the team has been assembled and organized, it must decide on its first project. One of the primary factors for the team's first project should be the prospect for quick and successful completion. There are several reasons for this. First, the initial project will be a learning experience in working as a team, analyzing changeover, and then implementing changes. A relatively simple project allows the team to focus on getting the process in place. Second, if the team initially gets bogged down in a long and difficult process, members may get discouraged. A quick "victory" gives the confidence that comes with success and is a powerful motivator. Finally, management always likes to see results. Rapid completion of a project, even if relatively small and simple, will build credibility for the team in management's eyes.

Once the team has gained confidence in their ability to work through a changeover improvement, they can move on to more complex or longer-term projects.

In analyzing changeover, a common difficulty stems from looking at the overall changeover. The problem with this approach is that it may be hard to see the trees for the forest. Changeover improvements will usually be the result of many small improvements rather than a single large improvement. To find the opportunities for small improvements, the changeover needs to be broken down into its smallest possible elements. Video analysis is one way to do this.

The Heisenberg Principle states that observation of an event changes the nature of the event. This holds true in changeover as well. If a person is watching the changeover, the mechanic will likely work differently than if the changeover is done normally. Use of a video camera does not completely eliminate this concern, but as it tends to be less intrusive, it does reduce it.

An even more important factor in favor of the use of video is that it can be viewed over and over again to get down to the finest level of detail.

The video does not need to be an Academy Award production, but there are some basic steps that need to be followed:

- The entire changeover must be taped. This includes the whole process starting with clean-up through set-up and

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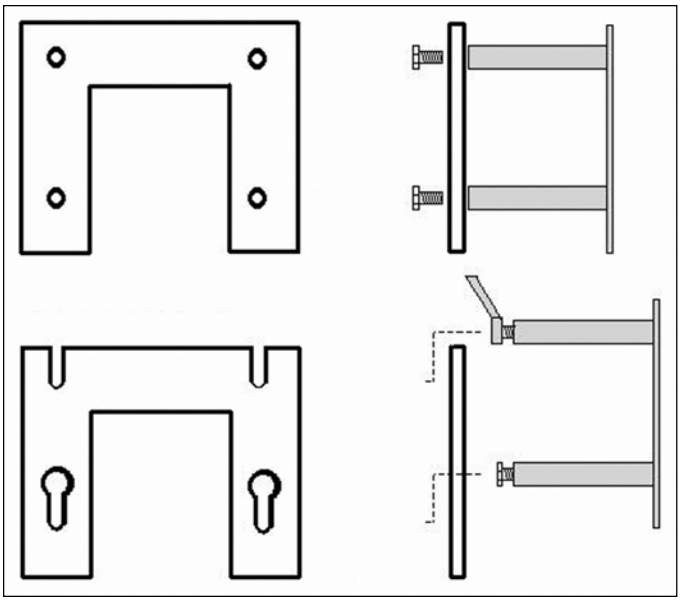

Figure 4. Slots and keyholes.

start-up. The tape must be left rolling the entire time to allow determination of the actual changeover time. In other words, if the changeover people go off to look for a part, leave the tape rolling. The only exception would be if a normally scheduled break such as lunch occurs. At this time the camera should be shut off until the team returns.

- The on-screen clock on the camera should be on to allow precise timing of each element.

- The camera may be mounted on a tripod with a good overview of the line or machine being analyzed. It may be necessary to get in close to film some details, but generally if the camera shows, say, a mechanic removing the chucks from a capper, someone on the team will be able to flesh out the details what is happening.
- It may be necessary to use several cameras or video several changeovers to capture the entire process.

- The changeover being taped must be a normal changeover. If abnormal events occur during the process, the changeover should be refilmed.

Once the team has a good video, it will go to work deconstructing it. Each element of the changeover must be identified and listed in the smallest detail. The easiest way to do this is via a tabular sheet as shown in Figure 2. If the mechanic removes a bolt, this element needs to be listed. The video should be gone over several times until the team is sure that they have identified and listed everything that takes place.

Each element on the list then needs to be analyzed and classified in one of four categories (listed in decreasing order of priority):

Eliminate - Is it really necessary to adjust both conveyor rails? Mechanics generally like to center the bottle on the conveyor, but the fact is that in most cases, it will run just as well off center. If only one rail is to be adjusted, it will cut the total adjustment time in half.

Externalize - Remember, the key is not so much reducing the total amount of labor as reducing the length of time the line is down. One way to reduce downtime is to externalize tasks to the maximum extent possible. "Externalization" means performing changeover tasks either before or after the changeover, "externally" to the changeover time. One common activity that takes place during changeover is that the technician will go to collect the various change parts required. If this is done during the changeover, it will extend changeover time. This is something that can be done ahead of time so that all the required parts are available the moment they are needed. A changepart cart to organize and transport the parts will be very helpful. See Figure 3 for an example from a blister-packing machine.

Simplify - Any elements that cannot be eliminated or externalized need to be simplified where possible. This will include the elimination of tools, use of slots and keyholes, quick connectors, and the like - *Figure 4*.

As part of simplification, all adjustments must be made measurable. This may be done with digital position indicators (Figure 5), scales, scribe marks, or the like. Gauges also may be used, but as these are a "tool," should be avoided wherever possible.

No Change - Finally, there will be many elements where no improvement is possible. This is okay, but they need to be identified as such. Periodically, they should be re-examined in case process changes, new ideas, or new technologies allow improvement.

Once each element has been classified, they need to be prioritized as A, B, or C. An A item is something that can be done immediately. Replacing bolts with handknobs on conveyor adjustments, for example. B items require a bit more to implement due to personnel requirements, budgets, or the like. Finally, C items are the truly long-range items. They are justified, but for various reasons will be difficult to implement. A C item might be the replacement of a major piece of machinery with one that is more changeover friendly.

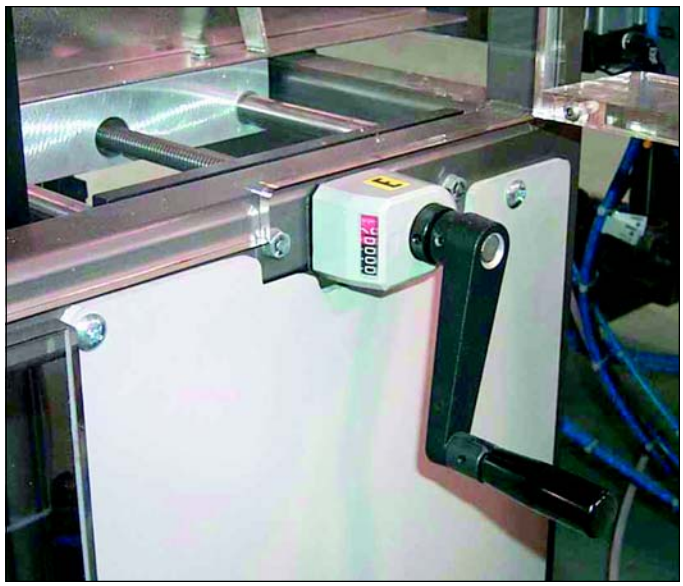

Figure 5. Digital position indicators.

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> ***Successful reduction requires a conscious and above all an organized effort.***

Unimplemented, all of the above is nothing more than a good intention. Once items have been identified and prioritized, they must be implemented. The team must develop an action plan including assignment of specific items to specific team members and a target date for completion. Team members should then report the status of each of their assignments at each meeting.

Conclusion

Edward Deming reportedly once said of Statistical Process Control, "I don't claim that it is easy, but I do claim it will work." He could have been speaking of changeover. Reducing changeover time is often difficult. The cost of downtime is so high that changeover reduction is almost always justified. Successful reduction requires a conscious and above all an organized effort. Informal attempts will usually produce some results, but will generally only find the really obvious opportunities.

A formal, dedicated program with management support is required. An effective program will choose the appropriate team members, train them in appropriate analytical procedures, and provide them with the tools they need for success. This article has attempted to provide a starting point for the process.

About the Author

John Henry is an internationally recognized "Changeover Wizard," and through his company, changeover.com, consults and trains on the subject. Henry has more than 25 years of experience in pharmaceutical packaging, manufacturing, and automation. He was formerly Manager, Facility Operations, for Alcon Laboratories' Puerto Rico facilities. Since 1985, Henry has been engaged in the conceptualization, specification, design, sales, installation, troubleshooting, and support of automated packaging and manufacturing systems. He has acquired particular expertise in the area of changeover. He has published numerous articles on the subject and is a popular conference speaker. Henry holds a masters degree from InterAmerican University with a double concentration in interpersonal relations and industrial management. Since 1982, he has been adjunct faculty with Southern New Hampshire University teaching in the MBA program. He is a Certified Packaging Professional (CPP) and a long time member of the Institute of Packaging Professionals (IOPP) where he serves on both the national board and the Packaging Equipment Performance technical committee.

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Ensuring Measurement Integrity in Validation of Thermal Processes

by Göran Bringert

Introduction

The integrity of temperature measurements is a critical part of validation of thermal sterilization processes. It is important that the validation SOP reflects the theoretical and practical aspects of how to achieve and maintain high accuracy temperature measurements in conjunction with thermal validation.

Heat Penetration Studies are performed to calculate the accumulated lethality, F_0, in the load. The accumulated F_0 is the time integral of the lethality function:

$$L = 10^{\left(\frac{T-Tb}{z}\right)}$$

At a base temperature T_b = 121°C and z = 10°C, the effect of 1°C error in measured temperature at 121°C results in approximately 25% error in the lethality calculation.[1]

FDA Definition of Process Validation:
Establishing by objective evidence that a process consistently produces a result or product meeting its predetermined specifications.

The required temperature uniformity in the chamber, according to regulations[2] and industry standards, should be better than or equal to 1°C or 0.5°C depending on the application. The instrument, including temperature sensors, used for validation measurements should be at least three times as accurate as the process variable measured.[3] This means that the Overall System Accuracy should be better than or equal to ±0.33°C or ±0.17°C, respectively.

Regulatory Requirements

FDA - GMP

Total System Accuracy better than ±0.5°C per proposed cGMP (1976) Total System Accuracy includes recorder, sensors, and calibration references and standards.

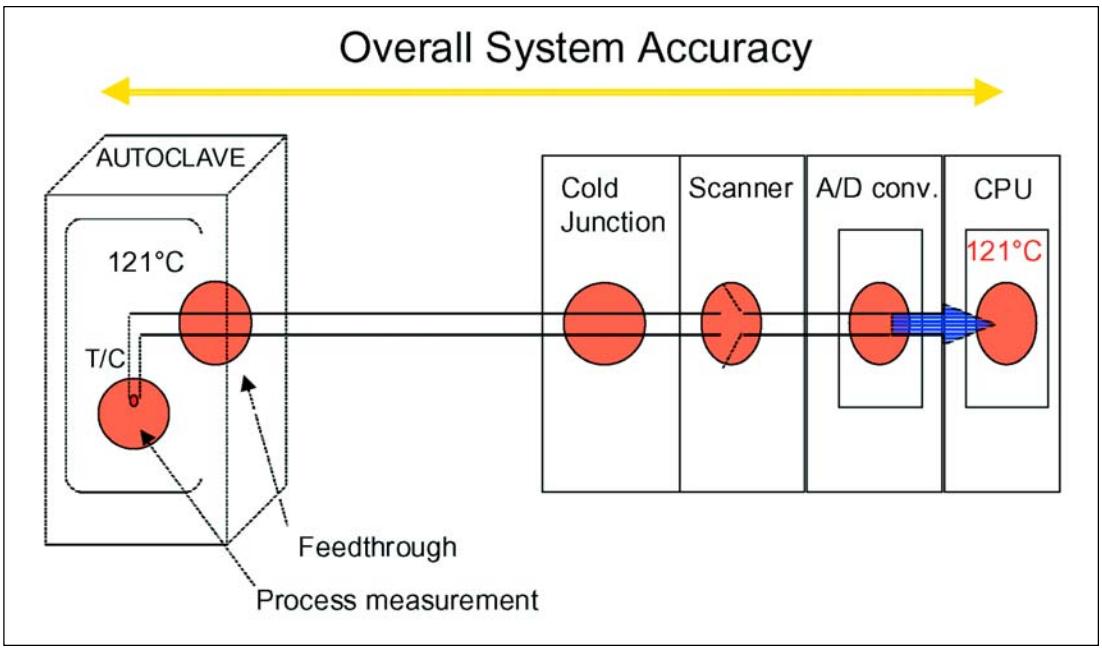

Figure 1. The measuring chain is composed of all components involved in the measurement.

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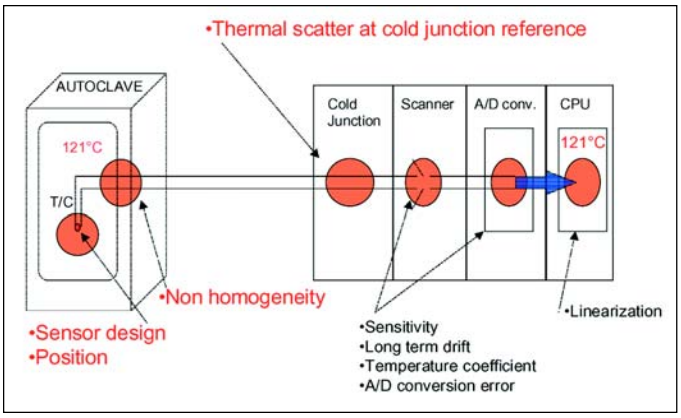

Figure 2. Random and systematic error sources in the measuring chain.

HTM 2010

The repeatability of the test equipment should be ±0.25°C or better, and the limit of error of the complete measurement system (including sensors) should be no more than ±0.5°C.

EN 285 - 26.4.5

The limit of error between 0°C and 150°C (excluding temperature sensors) shall not exceed ±0.25% (±0.375°C of full scale).

EN 554 - 4.6.2

The accuracy of test equipment shall be not less than the accuracy of the instruments fitted to the sterilizer, and shall exceed by *at least a factor of three* the accuracy of measurements required to judge the performance of the sterilizer.

EN 554 Annex A (informative) - A.2.6

The factor of three was chosen because it provides approximately a 1:10 guarantee that any error noted in readings is not caused by the inaccuracy of the test instrument.

Error Sources

Several variable error sources can affect the temperature measurement accuracy in validation. Control and management of these error sources should be recognized as the responsibility of the people who perform the validation. Individuals responsible for validation should have the competency to adequately perform the validation studies.

It is important to distinguish between systematic and random errors. Systematic Errors are eliminated by calibration which, will be discussed later. Random errors are not eliminated by calibration, and can only be minimized through applying knowledge and proper procedures. The operator has to understand how to minimize the influence of random temperature measurement errors to consistently achieve the accuracy required for thermal validation of steam sterilization processes. Procedures documented in the validation SOP and individual training of validation personnel is necessary to maintain competency of the validation team.

Electronic temperature measurements for validation are acquired using temperature sensors connected to an electronic datalogger or recorder.

All components involved with the measurement, (from the tip of each sensor, via the connecting wires, cold junction reference, signal interface, analog to digital conversion, conversion from millivolts to temperature, to display and printout of the measured values) are referred to as the Measuring Chain. Figure 1 shows a Measuring Chain using thermocouples.

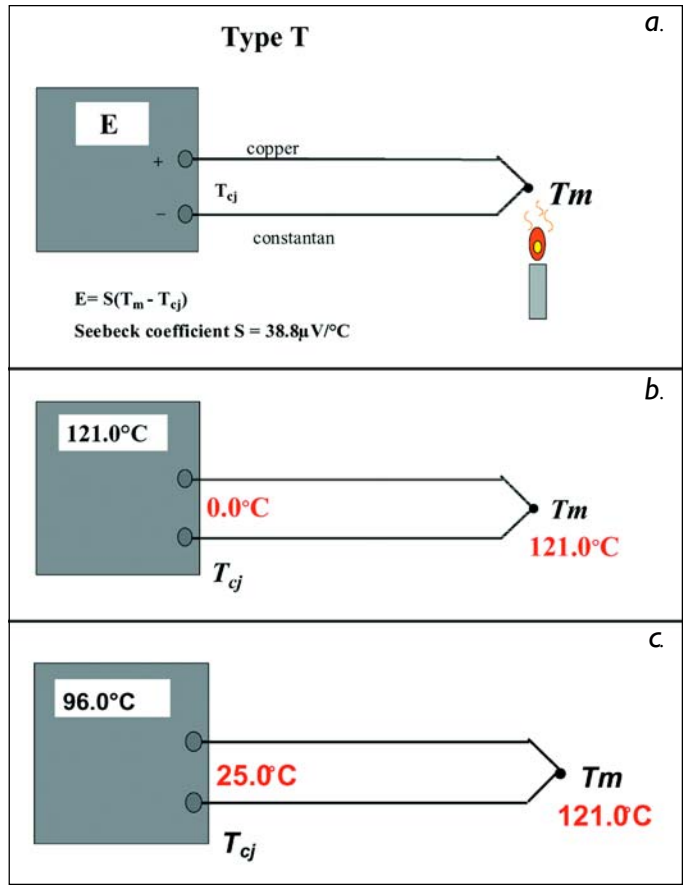

Figure 3.

The components of the Measuring Chain contribute errors, systematic or random, that contribute to the Overall System Accuracy. Figure 2 identifies the most significant Random Error Sources (in red) in the Measuring Chain.

Significant random errors can occur in the following areas:

- ***Sensor and Circuit***
  Sensor design and location
  Nonhomogeneity

- ***Measurement System***
  Thermal scatter at the cold junction reference

Temperature Sensors

Temperature sensors used for control and monitoring are:

- Thermocouples
- Resistance Thermometers (RTDs)

Direct and indirect liquid expansion thermometers may be found on older sterilizers, but have been replaced by electric temperature sensors on newer sterilizers.

With modern technology, thermocouples and RTDs can deliver equal accuracy. However, validation is a portable application where sensors are significantly abused—dropped, wound up, tied, stepped on, and rolled over. Because RTDs are sensitive to physical shock, it is very difficult to maintain accurate and repeatable results with them if used for validation. In addition, an RTD should have a four-wire design, which provides two leads for the sensor excitation and two leads for measuring the voltage difference across the resistor

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to eliminate resistance changes in the lead wires. Thermocouples are sturdy, except for work hardening, need only two wires, and require no external excitation. Therefore, thermocouples are the preferred sensors for validation. RTDs are commonly used as built-in sensors for process control purposes.

Accurate temperature measurements with thermocouples require proper design and installation of the thermocouple circuit. If possible, a continuous length of stranded homogeneous wire should be used from the measuring junction to the terminals of the measuring system. When two or more sections of wire are required by operational considerations, the connections between the sections must be in locations where the temperature in the circuit does not change significantly along its length. Ideally, all sections of wire should be from the same production lot. If that is not practical, the wire should be selected to have the best interchangeability possible. The accuracy of thermocouple measurements depends largely on how well the cold junction compensation is carried out. Validation systems are designed to provide high accuracy cold junction compensation, while standard process controllers lack the cold junction compensation accuracy needed for validation purposes.

Thermocouple type T (copper/constantan) is the most commonly used thermocouple for temperature measurements in validation applications due to its high accuracy and low cost.

Simplified Thermoelectric Theory

A thermocouple directly produces a voltage that can be used as a measure of temperature. That terminal voltage used in thermometry results only from the Seebeck effect.

The Seebeck Electromotive Force (emf) is the internal electrical potential difference or electromotive force that is viewed externally as a voltage between the terminals of a thermocouple. This Seebeck source emf actually occurs in any electrically conducting material that is not at uniform temperature even if it is not connected in a circuit. The Seebeck emf occurs within the legs of a thermocouple. It does not occur at the junctions of the thermocouple as is often asserted nor does the Seebeck emf occur as a result of joining dissimilar materials as is often implied. (From: Manual on The Use of Thermocouples in Temperature Measurement; ASTM Manual Series: MNL 12, 1993)

The Seebeck coefficient of a single material is always given relative to some reference material. Standard reference material is Platinum-67. The Seebeck coefficient of any pair of conductors is equal to the difference of the Seebeck coefficients of each conductor relative to the standard reference material.

A type T thermocouple is made of copper and constantan. The Seebeck coefficient for copper relative to Pt-67 is +5.9µV/°C at 0°C and that of constantan is -32.9µV/°C, the Seebeck coefficient for a type T thermocouple at 0°C is 38.8µV/°C - *Figure 3a*.

All thermocouple tables correlating emf to temperature are based a cold junction temperature of 0°C - *Figure 3b*.

If the cold junction T_{cj} is at any other temperature than 0°C, the emf generated over the leads of the thermocouple will result from the difference in temperature. An indicating instrument would then display the wrong temperature value - *Figure 3c*.

A cold junction compensation voltage proportional to the actual temperature T_{cj} is needed to enable accurate temperature measurements with the cold junction at ambient tem-

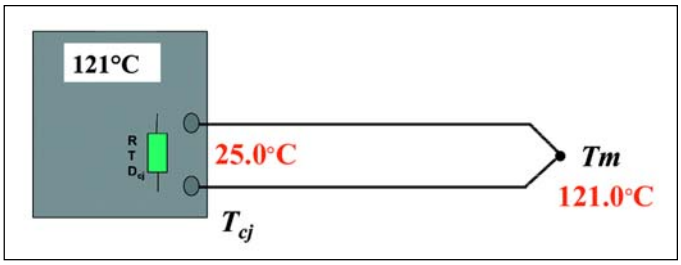

Figure 4.

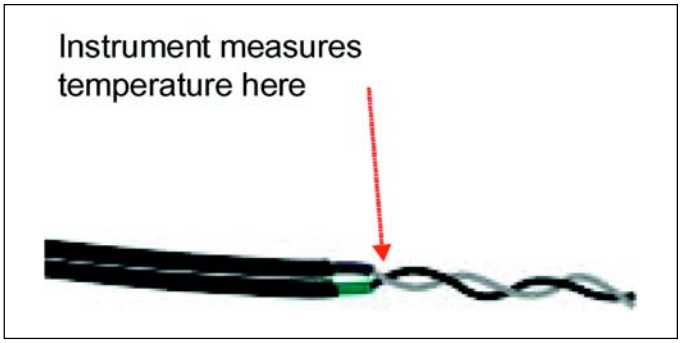

Figure 5. Twisted thermocouple.

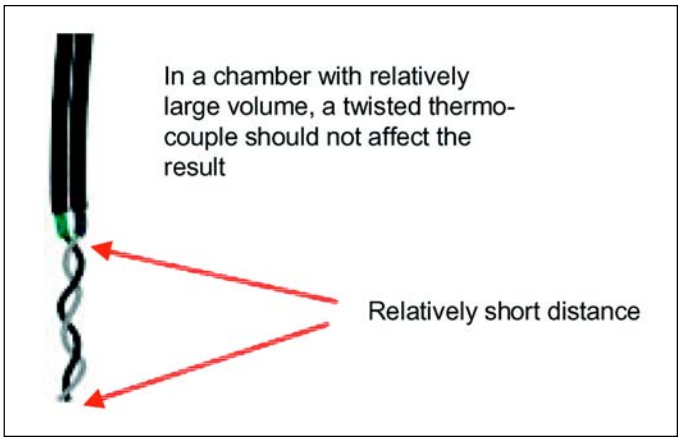

Figure 6. Chamber with large space.

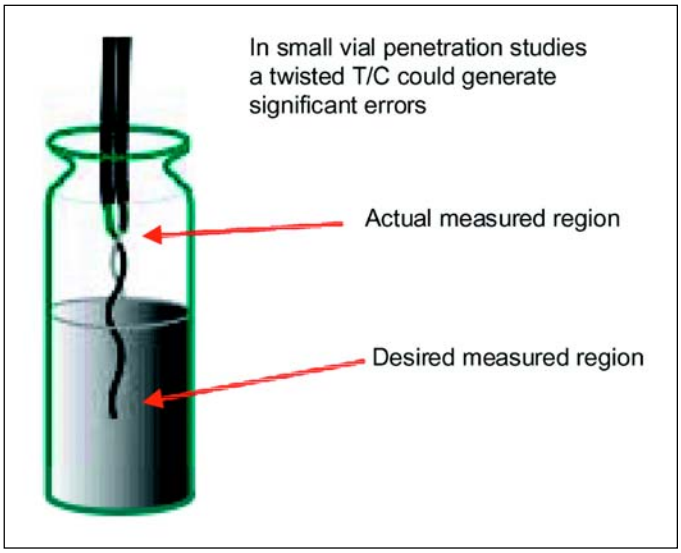

Figure 7. In a small volume for penetration studies, a twisted thermocouple could generate significant errors. Indicated temperature somewhere between the two regions.

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perature. Modern measuring instruments monitor Tcj using an RTD at the terminals. The instrument calculates the difference between the actual temperature at the terminals and 0°C and adds that value to the voltage from the thermocouple and displays the correct temperature - *Figure 4*.

Sensor Design

The temperature sensor should be designed for the application. A sensor designed for measuring the temperature in a LVP bag cannot be used for measuring the temperature in a 1 ml ampule. Several factors have to be considered when specifying the design of a temperature sensor for a particular application.

Regardless of how many facts are presented herein and regardless of the percentage retained, all will be for naught unless one simple important fact is kept firmly in mind. The thermocouple reports only what it "feels." This may or may not be the temperature of interest. Its entire environment influences the thermocouple and it will tend to attain thermal equilibrium with this environment, not merely part of it. Thus, the environment of each thermocouple installation should be considered unique until proven otherwise. Unless this is done, the designer will likely overlook some unusual, unexpected, influence.
(From: Manual on The Use of Thermocouples in Temperature Measurement; ASTM Manual Series: MNL 12)

Examples:
Size - A long or large sensing element will report an average temperature over the length of the element. In penetration studies, a small sensor will give a more true reading of the cold spot.

Shape - A sensor for measuring surface temperature needs to be flat and adhere to the surface.

Response time - The size of the temperature sensor should be small relative to the object being measured in order to minimize the influence on the thermodynamic properties of the object. The response time of the sensor is size and mass dependent. The response time should be at least five times shorter than the fastest rate of change in the process to be recorded in order to give a true representation of the process dynamics.[4] This is especially important for determination of D and z values using ampules in BIER vessels.

Heat conduction - The copper wires in type T thermocouples can conduct heat into or out of the temperature sensor depending on the cross sectional area of the copper wire, and the temperature difference between the tip and the environment.[5]

Sensor position - The temperature sensor reports the temperature it "feels". Therefore, the sensor must be positioned in an unambiguous thermal environment.

- A sensor measuring temperature distribution in a sterilizer must be freely suspended in the chamber. If the sensor touches the chamber wall, it will report some temperature that lies between the actual chamber temperature and the temperature of the chamber wall.

- A sensor measuring heat penetration must be fixed in position relative to the walls and content of the container.

Thermocouple Specifics

Twisting bare wires together increases the contact between the leads over the length of the twisted portion. The instrument measures the temperature at the first point of contact, i.e., the furthest point from the tip - *Figure 5*.

Using a twisted thermocouple to measure air temperature in a steam sterilizer would not significantly affect accuracy because the difference in air temperature between the tip and the last point of contact is negligible - *Figure 6*.

However, twisted conductors could produce incorrect data

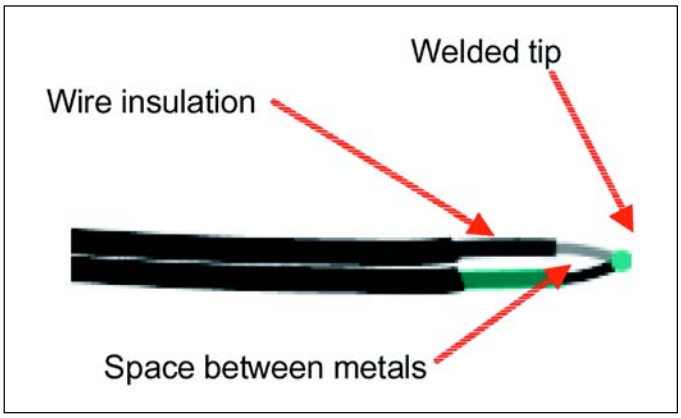

Figure 8. A thermocouple with welded tip provides secure contact at a single point, allowing it to be used in many different applications.

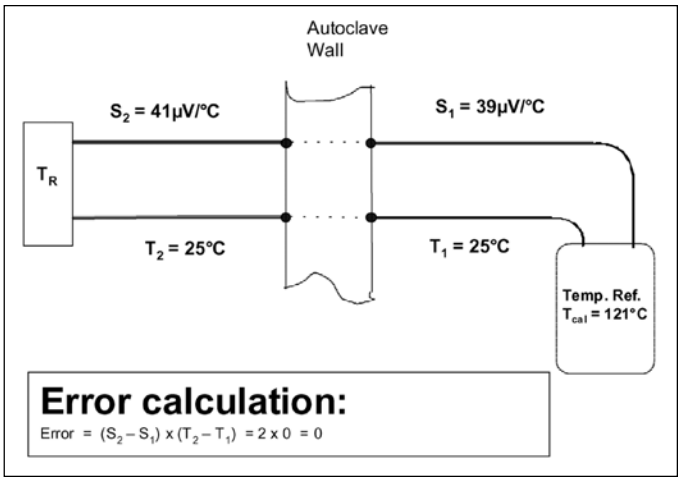

Figure 9. Nonhomogeneous region during calibration.

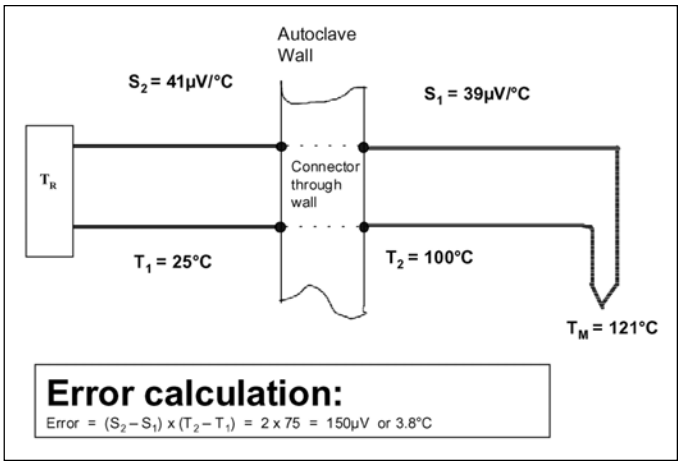

Figure 10. Nonhomogeneous region during validation.

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when the thermocouple is used to measure the temperature of liquid in a vial. Inserting this thermocouple (Figure 7) causes the instrument to indicate a temperature somewhere between the air and liquid temperature.

Avoid this problem by reducing the junction to the smallest practical size. Use an argon welder to create a thermocouple junction, resulting in a small bead that joins the wires at the tip - *Figure 8*. Strip the wires no more than necessary to create a weld. The insulation that is left on each wire separates the unwelded bare lengths of wire.

Nonhomogeneous Regions[6]

The thermoelectric power of a conductor is a function of the composition and structure of the material. Connectors, extension wire, and repetitive flexing (work-hardening) will cause nonhomogeneous regions in the thermocouple circuit. A nonhomogeneous region that is located in an area with large temperature gradient, e.g. the sterilizer wall, will generate an error that cannot be eliminated by calibration. Random errors caused by nonhomogeneous regions can exceed 4°C7. If possible, a continuous length of stranded homogeneous wire should be used from the measuring junction to the terminals of the measuring system. When two or more sections of wire are required by operational necessity, the connections between the sections must be in locations where the temperature in the circuit does not change significantly along its length. Ideally, each section of wire should be from the same production lot. Thermocouple extension wire should not be used.

The principle of errors generated by nonhomogeneous regions in combination with a temperature gradient is illustrated in Figures 9 and 10. The nonhomogeneous region does not generate an error during calibration as T1 = T2.

During the validation study (Figure 10) a temperature gradient exists across the wall of the sterilizer. An error is generated due to the difference in Seebeck coefficient between the thermocouple wire and the connector. Calibration cannot eliminate this error. The gradient $T_2 - T_1 = 75°C$ in this example generates an error of 3.8°C during the validation study.

Insulation

Teflon insulated temperature sensors with properly sealed tips are suitable for temperature measurement in steam sterilizers. Teflon does not leave particulates behind in the sterilizer. Teflon wire is rated for continuous use up to 200°C, with a peak rating of 260°C. Using it at higher temperatures will melt the insulation and create toxic gas.

Kapton insulated temperature sensors are used for dry-heat applications ranging from 150 to 375°C. Kapton insulation is wrapped around the thermocouple wires and bonded in place. The higher the temperature, the faster the bonding will degrade and the Kapton insulation will unravel. For example, the life of a Kapton insulated temperature sensor, operating at 300°C vs. 375°C, goes from several months at 300°C to less than six days at 375°C. Kapton will not leave particulates in the sterilizer or tunnel like fiberglass and ceramic insulation.

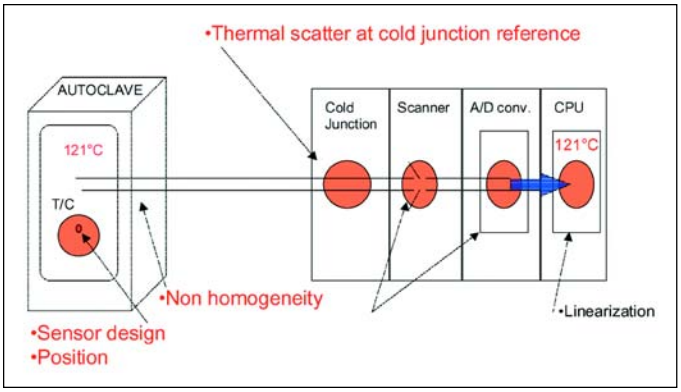

Figure 11.

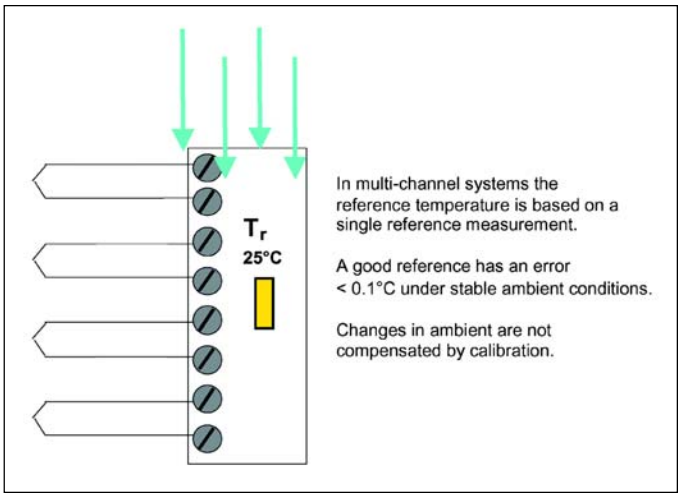

Figure 12. Thermal scatter on the cold junction terminal. In a multipoint thermocouple system, the reference temperature is based on a single measurement.

Measuring System Errors

A change in ambient temperature is the most significant source of error in thermocouple measuring systems, particularly in multi-channel systems with internal cold junction references. All modern instruments for thermocouple temperature measurements have an electronic circuit for determining the temperature at the terminals to which the thermocouples are attached, the Cold Junction Reference (Figure 9). The Cold Junction Reference temperature will only be correct for all thermocouples under steady state ambient temperature conditions and a system completely warmed up. A sudden change in ambient temperature, e.g. air draft, will cause

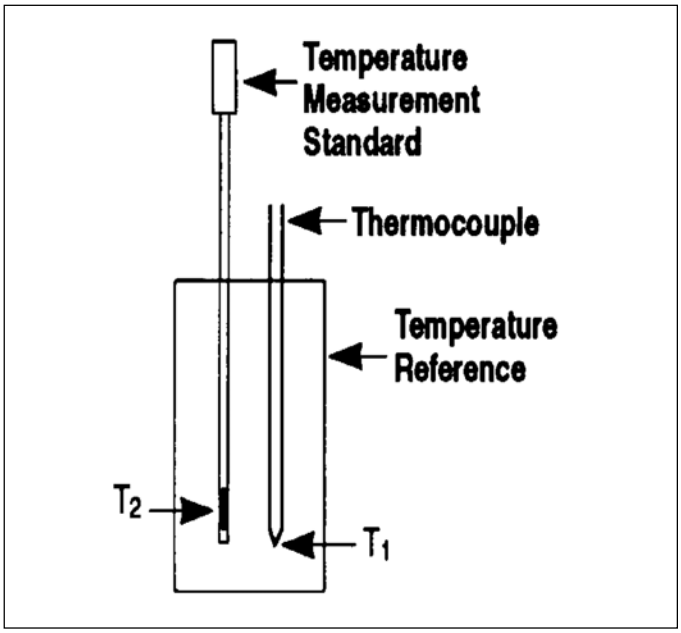

Figure 13. Transfer calibration error is the temperature difference between thermocouple tip. (T1) and the measurement standard (T2).

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thermal scatter at the cold junction terminal. This thermal scatter produces an error that is equal to the relative change in temperature between the reference point and each thermocouple terminal. Keep the cold junction terminals covered and maintain the ambient temperature conditions during the validation study.

Accuracy

It is important to distinguish between relative and absolute accuracy. In many processes relative accuracy is sufficient, but in thermal sterilization processes absolute accuracy is essential.

Relative Accuracy

The ability of the total system to repeat a given measurement or compare several measurements. Relative accuracy depends primarily on the quality of the sensors, measuring system employed, and how the system is installed.

Absolute Accuracy

The ability to determine the value of a parameter relative to standard accepted values. Absolute accuracy can be achieved only by calibration of a system relative to accepted and recognized standards. Absolute accuracy depends not only on the sensors and the installation, but also on the calibration standards and calibration technique.

Calibration

Thermocouple systems used to measure temperature in the validation process should be calibrated before and verified after each use. Typically, neither the measuring system nor the thermocouples will change their characteristics between calibration, but the calibration process ensures proper operation of the entire system. Because corrections applied to each thermocouple also include the errors of the measuring system, each thermocouple must be connected to the same channel in calibration as in the validation study. To the extent possible, the entire system should be calibrated under the same ambient temperature and conditions as it will experience during operation. Ideally, the calibration should be carried out with the temperature reference next to the sterilizer to be validated,

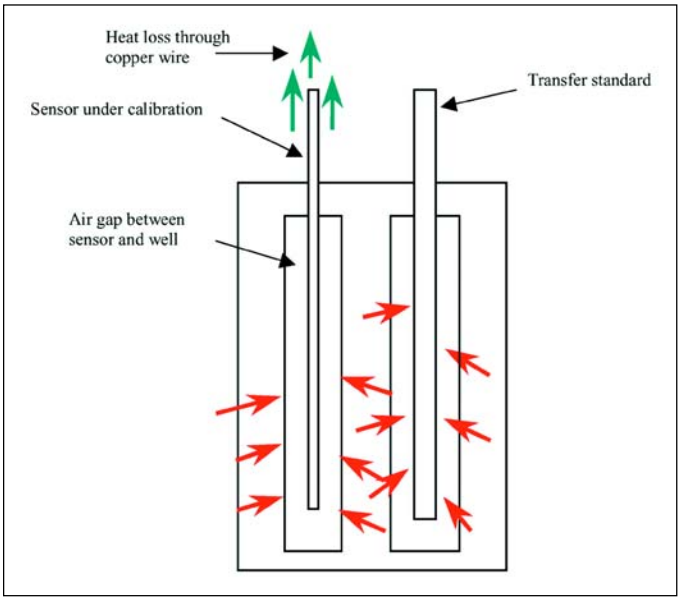

Figure 14. Stem conduction causes heat loss and generates calibration error.

provided the design of the validation system makes it practical.

When calibration is performed next to the sterilizer, it is practical to use two traveling transfer standards for calibration. This is to reduce risk. Using two transfer standards for calibration is an insurance against rejecting an entire study in the event the instrument was out of tolerance. It is unlikely that both standards might be damaged in the same way at the same time. If one transfer standard goes out of calibration it will not agree with the other and should alert the operator of a calibration error. The traveling transfer standards have to be verified against a stationary transfer standard at regular intervals specified in the calibration SOP. Metrological praxis is to have two stationary transfer standards against which each traveling transfer standard is verified.

Calibration Basics

There are a few basic rules that should be followed in any calibration procedure.

Challenge all results. No single measurement should be accepted as being correct unless it is verified by other results.

Be patient. A frequent mistake in calibrating instrumentation is to take measurements and make adjustments before conditions have stabilized. It may take much longer than expected for a system to become completely stable, because thermal equilibration takes place exponentially and the output may seem to be stable even though it is still changing slowly.

The accuracy of the transfer standard must be better than that of the instrument being calibrated. This would seem obvious, but it is amazing how often a voltage calibrator is used that has a greater error than the system being calibrated. It is important to recognize that the accuracy of the calibration can be no better than the standard used, and it is a mistake to change the adjustment of a measuring system if it is already more accurate than the standard.

The characteristics of the transfer standard must have been determined by a procedure that is traceable to accepted primary standards. In the United States, the National Institute of Standards and Technology (NIST) is the accepted source of primary standards. The transfer standards need to be calibrated by NIST relative to their primary standards or by a qualified Standards laboratory relative to standards calibrated by NIST. In either case, the test results and test numbers should be known so the calibration procedure can be traced to the primary standards.

The transfer standard must be independent of the measuring system. Because the output of a thermocouple depends on the entire circuit, it is not a desirable transfer standard. A resistance temperature detector (RTD) is a device that indicates changes of temperature by a change of resistance. Because the resistance of an RTD is only a function of its temperature, and the resistance can be measured independently of the system being calibrated, RTDs are ideal temperature transfer standards.

The transfer standard must be stable in shipment and tolerate other handling. As its name implies, the purpose of the transfer standard is to transfer a measured characteristic from one laboratory to another. The characteristics of the standard must be the same when received from NIST as when it was calibrated relative to their standards. Liquid in glass thermometers may be damaged or develop small voids in the liquid during shipment, and therefore are not reliable temperature transfer standards. RTDs are sensitive devices that maintain

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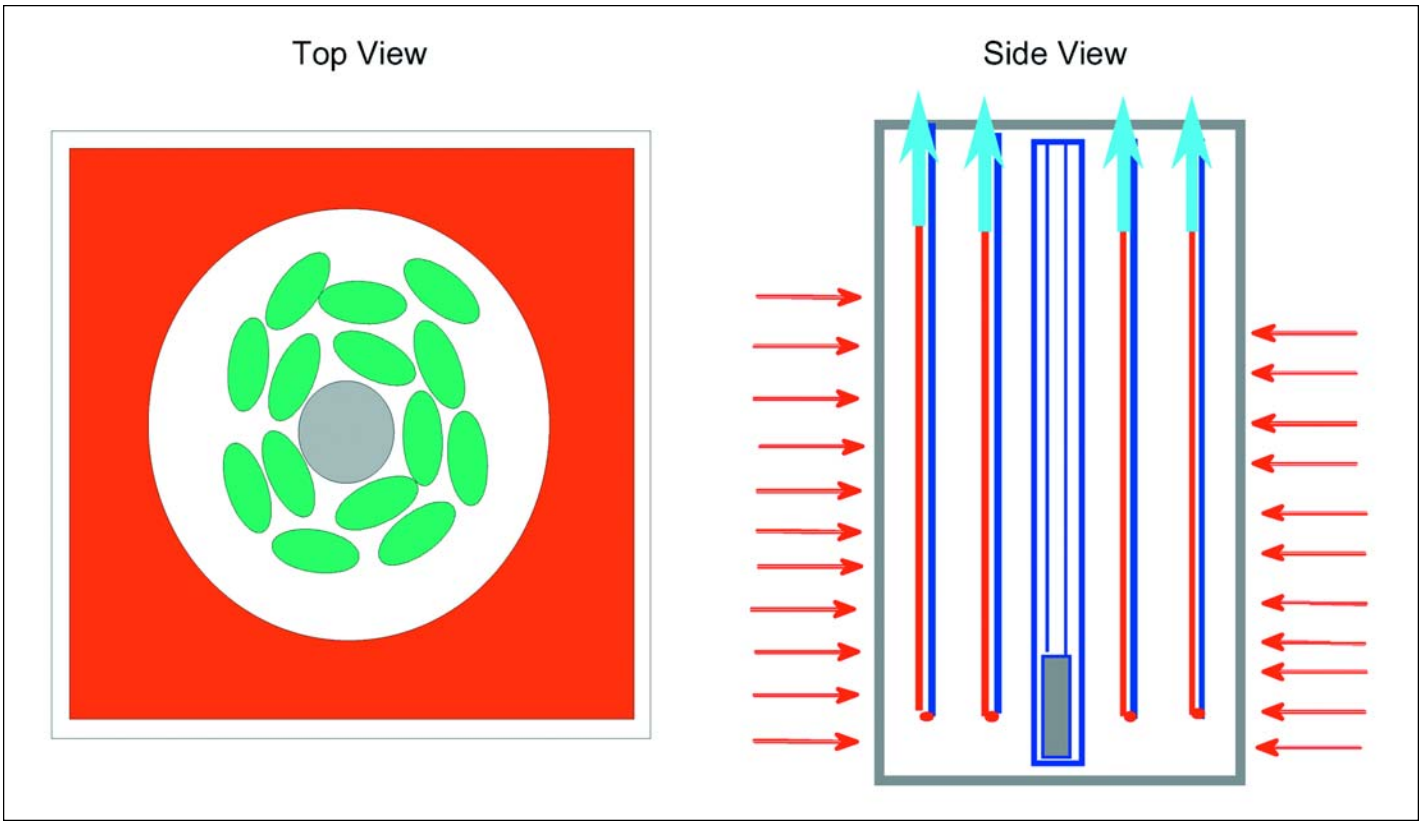

Figure 15. View of dry block with one large well and no insert.

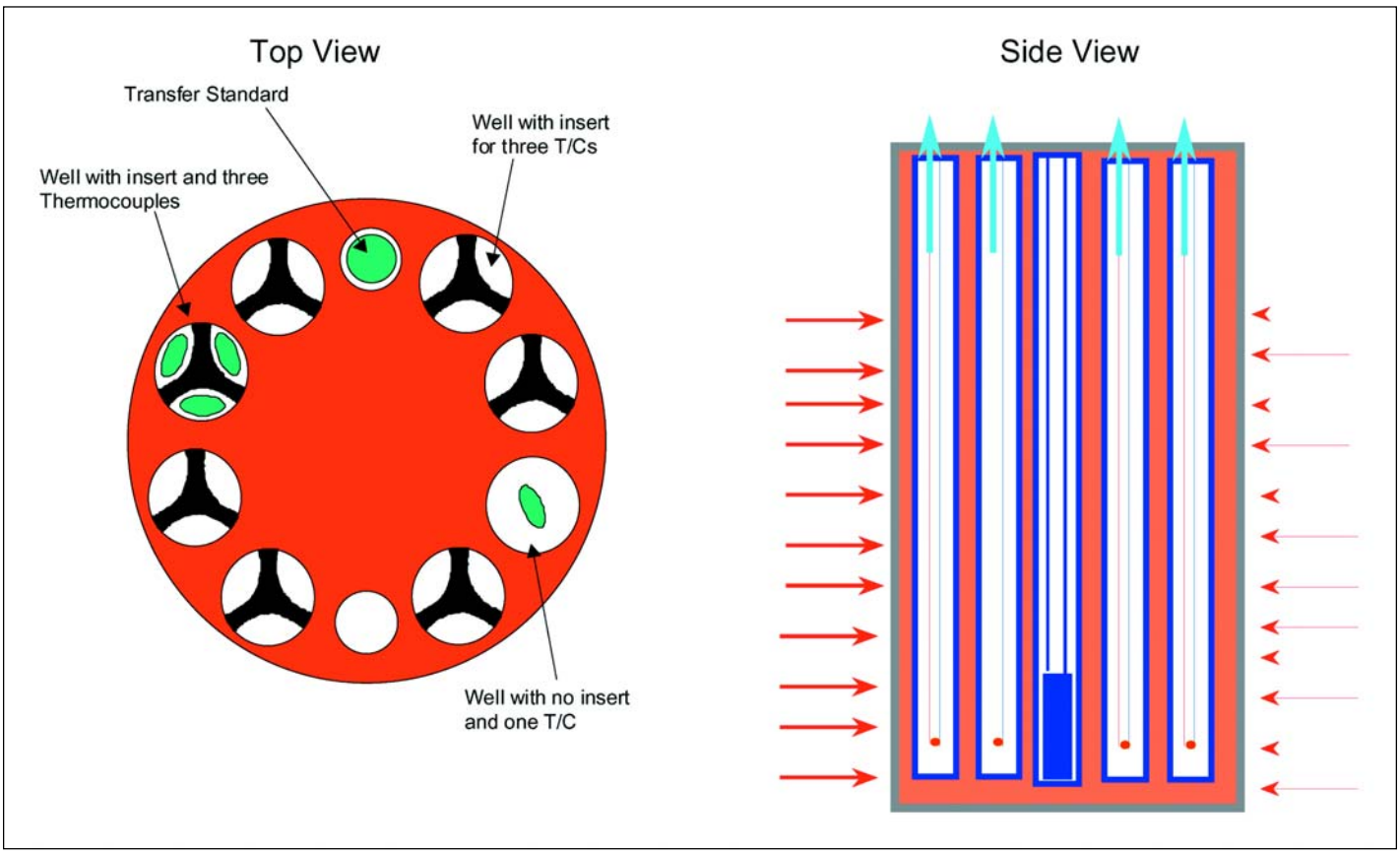

Figure 16. View of dry block with inserts to minimize air-space around sensors.

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their characteristics only with careful handling and shipment.

ISO 10012 - 1:1992 Metrological confirmation system for measuring equipment, states in section 4.3 Confirmation system - Guidance… The error attributable to calibration should be as small as possible. In most areas of measurement, it should be no more than one third and preferably one tenth of the permissible error of the confirmed equipment when in use…[8]

Temperature Reference

Significant random calibration errors that can occur in a dry block temperature
reference:

- Transfer Calibration
- Stem conduction
- Uneven heat transfer
- Immersion depth
- Well inserts not used
- Stability
- Time needed for stabilization

Reference Error, Using Thermocouples

When calibrating a thermocouple T1, against an RTD transfer standard T2, a key contribution to error is the difference in temperature between these devices when placed in the reference - *Figure 13*. This difference is called *transfer calibration error* and is potentially the largest contribution to calibration errors in dry block references. Transfer calibration error contains two components:

- Stem conduction error, which cools the thermocouple tip - *Figure 14*
- Uniformity of the reference wells relative to the standard well.

Stem conduction error is affected by the parameters listed below. Some are inherent in the reference design while the user can reduce others.

- Sensor depth in the well
- Lateral thermal conductivity between medium and sensor wiring
- Wire gage and material of thermocouple wire
- Temperature difference between medium and ambient

Reducing Stem Conduction Errors

To minimize stem conduction errors in a dry block temperature reference:

- Use thin (27 gage or less) thermocouple wire as it contains less thermal cross section to draw heat from the tip.
- Have sufficient well depth to keep tip away from ambient. Stem conduction errors decrease exponentially with depth. Tips should be at bottom of well.
- Use inserts to bring sensor wires closer to the block for better lateral heat transfer. Thermal conductivity to the well sides improves with the decrease in air space around the sensor wires - *Figures 15 and 16*.

Dry block design can have a significant influence on transfer calibration errors. A dry block with large diameter wells does not conduct heat evenly into each sensor under calibration. Bundled thermocouples shield each other from the heat, increasing the effect of stem conduction more significant - *Figure 15*.

A dry block with smaller diameter wells and inserts provides closer thermal coupling between well walls and sensors under calibration, minimizing the effect of stem conduction and transfer calibration error - *Figure 16*.

A dry block designed for maximum transfer calibration accuracy has small diameter wells with inserts that fit the size of the sensors under calibration - *Figure 16*.

Calibration Procedure

Calibration of the Measuring Chain (Figure 1) should be done with the sensors connected to the data logger/recorder and installed in the sterilizer via the feed thru and out through the open sterilizer door. The sensors should be inserted into the temperature reference bath or dry block, just outside the open sterilizer. Calibration should be performed prior to a validation study and a calibration check should be performed at the conclusion of the validation.

Pre-Study Calibration

A two-point calibration should be used with calibration points bracketing the sterilization temperature for the process under validation, e.g. 100°C and 130°C, and calibration checkpoint should be, e.g. 121°C, between the two calibration points to verify the calibration.

Post-Study Verification

A two-point comparison between the temperature standard and the temperature sensors should be performed to verify that the calibration of the measuring chain is intact.

The calibration should be documented, to provide evidence that the temperature of the reference, the transfer standard, and the sensors were stable before the determination of *calibration correction values*. The calibration documentation should include data on the deviation between the temperature standard and each temperature sensor before and after calibration. To ensure traceability, the documentation must list the calibration parameters and equipment including serial numbers and last calibration dates.

Error Budget

Different manufacturers state the accuracy of their thermocouple measuring systems in different fashions. Some give detailed breakdowns of the error sources; some simply state total error when operating within a limited range of ambient temperature. In any case, total system error must include the sum of all errors in the measuring chain.

An example of a detailed error budget is given below:

Measuring Chain Error Budget @ 121°C

Recorder		
Conformity Error	0.04	°C
A/D Conversion Error	0.01	°C
Total Cold Junction Ref. Error	0.10	°C
Total Recorder Error	0.15	°C

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Calibration Equipment	
Traceable Temperature Standard	0.025 °C
Reference Transfer Calibration Error	0.10 °C
Total Calibration Error	0.125 °C
Total Measuring Chain Error (Sum of worst case errors)	0.28 °C
RSS (Root Summed Squares)	0.15 °C

This level of detailed error budget specification is necessary to determine the adequacy of a measuring system for validation of thermal sterilization processes.

Summary

Validation of thermal sterilization processes requires accurate temperature measurements to provide reliable results. In order to ensure measurement integrity it is necessary that validation personnel has adequate training and well defined processes to follow.

References

1. PDA Technical Monograph 1.

2. cGMP, EN 285, EN 554.

3. EN 554.

4. Fundamental Process Control Theory, Instrumentation Society of America, 1981.

5. Probe Induced Errors, Clarence Kemper and George Harper, Pharmaceutical Technology, November, 1978.

6. R.P. Reed, 1998, Thermoelectric Inhomogeneity – Obscure Obstacle to Quality, in National Conference of Standards Laboratories, Albuquerque, NM 1998.

7. Clarence A. Kemper, Design, Installation, and Calibration of Thermocouple Measuring Systems, in Validation of Aseptic Pharmaceutical Processes, Chapter 5. Marcel Dekker, Inc., 1987.

8. ISO 10012 - 1:1992 Metrological confirmation System for measuring equipment.

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