

This article presents a statistical analysis of planning and execution strategies for Installation Qualification (IQ) and Operational Qualification (OQ) activities carried out in 50 construction/modification projects.

Best Practices for Qualification Success: A Statistical Analysis of Characteristics and Practices that Drive IQ and OQ Cost and Schedule

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Introduction

Installation Qualification (IQ) and Operational Qualification (OQ)¹ are frequently on the critical path of activities in the construction or modification of pharmaceutical production facilities. Any delay during the IQ/OQ phase is a major problem if it prevents product from being delivered to meet market demand and/or regulatory approval.

This article outlines the research that was conducted on how pharmaceutical companies carry out IQ and OQ activities. The research resulted in three major deliverables:

- statistical models that can be used to benchmark cost and schedule performance in the execution of IQ/OQ

- a list of key project characteristics that affect qualification cost and schedule
- a list of key Qualification Best Practices that drive qualification success and minimize qualification failure

Methodology

In this study, using ordinary least squares statistical regression methods, “uncontrollable” project characteristics and “controllable” project practices were reviewed for statistically significant links between them and what IQ/OQ costs and schedules were achieved.

Uncontrollable project characteristics are those which are inherent in the project scope and cannot be altered by the behavior of the project team. An example is the type of facility

being built (e.g., a bulk active pharmaceutical ingredient facility). Controllable project practices are those actions that the company management and the project team can choose to do or not to do. For example, the team could choose to develop a schedule of qualification activities during basic design instead of waiting until later in the project.

Table A. Characteristics of the research set.

Key Project Characteristic	Dataset(n = 50)
Facility Type	Bulk chemical active pharmaceutical ingredient: 21% Biological: 35% Oral dosage/Non-parenteral secondary: 25% Sterile formulation and finishing: 11% Other (incl. packaging facilities, pharmaceutical device facilities, etc.): 8%
Facility Scale	Production: 90% Pilot Plant: 10%
Project Type	Standalone (Greenfield or collocated): 57% Expansions: 33% Revamps/revisions/modifications of existing facilities: 10%
Geographical Location	North America: 49% Europe: 35% Puerto Rico: 8% Singapore: 8%
Product Description	Prescription: 94% Over the Counter: 6%
Project Engineering and Construction Cost (US\$ millions)	Mean: \$50 million Median: \$25 million Range: \$2.5-\$191 million

By seeking statistically significant links between project characteristics or practices and cost or schedule outcomes, an attempt was made to uncover those characteristics and practices that “drive” IQ/OQ cost and schedule.

Project Dataset

For the purposes of this study, data on 50 projects was collected from nine major pharmaceutical companies. The choice of “major” or what is often referred to as “big pharma” companies was not a deliberate effort to exclude medium or small companies. It simply reflects the fact that the data was collected from companies that were interested in participating in the research, and all interested parties happened to be major companies. The companies are not named because they wish to retain their anonymity. Data was collected using a customized questionnaire.² Some key characteristics of the set are shown in Table A. In order to be able to conduct an “apples-to-apples” comparison, the data for all 50 projects was “normalized” to a common cost baseline (currency, location, and year). In addition to asking project teams to complete a detailed questionnaire, each team was interviewed to verify the reliability of the data provided. In addition, each company chose to participate in the study in order to receive advance notice of results that would help them improve their estimating, planning, and execution of Commissioning and Qualification activities. Consequently, it was in the interests of each company to provide data that was as accurate as possible.

Analysis of Qualification Cost

Cost Data Limitations

When the project teams were interviewed in the course of the data collection activities, it was discovered that they used a wide variety of approaches in the recording of qualification costs. Variations in accounting were seen across companies and from project to project within companies. Project teams rarely recorded charges and hours for individual qualification activities, and owner participation in qualification was often not tracked or charged to projects. In some cases, qualification charges were “hidden” within equipment/vendor costs, project management costs, or in other capital costs for the project. Every effort was made to trace the costs. Where these costs were expensed and traceable to a specific account, they were collected and included. The methodology

Key Drivers	t-score	P > t
ln (TIC)	8.54	0.00
Biological Facility(Biological facilities vs. API, Oral, Sterile, and Other)	3.19	0.00
Pilot Plant Facility(Pilot Plants vs. all other facilities)	-2.10	0.04
Stand-alone Project(Stand-alone projects vs. Revamp and Expansion Projects)	2.01	0.05
Qualification Schedule Definition (Critical Path Method or Milestone schedules vs. No schedule planning/ end-date only)	-3.03	0.01

Table B. Relationship between key characteristics and practices and IQ/OQ cost.

was as follows: With the active advice and assistance of the study participants – it was decided what costs should be tracked and allocated as “qualification cost.” There are numerous project costs associated with qualification that may or may not be captured, for example, owner costs associated with approving protocols - which is often captured in the project management account. Once the decision has been made as to what costs will be allocated to this account, the process of normalizing from project-to-project, company-to-company is more straightforward. Therefore, while project cost data can be “messy,” the methodology used “forced” this messy data into defined “buckets” - a defined work breakdown structure that could then be analyzed in an apple-to-apples manner).

While “messy” cost information increases the variance in the data and the analyses, much of the error was essentially randomized across companies. Therefore, statistically significant industry outcome benchmarks still can be developed.

However, a major conclusion of this study is that the majority of project systems do not actually know exactly how much money is being spent for the completion of all the activities making up the total qualification effort.

IQ/OQ Cost Model

Given the limitations of the available cost data, the cost analysis for this study focuses on a single point of interest: the total cost required to complete IQ/OQ; (i.e., the cost to develop, write, and execute IQ/OQ protocols. All costs accrued by the owner, including internal and external (contractor/consultant) costs). While some commissioning and PQ cost data was available for some projects, the majority of projects were able to provide data for IQ/OQ only. Moreover, in the majority of cases, the IQ/OQ costs were not broken out from each other.

Project Size as an “Uncontrollable” Characteristic

IQ/OQ cost should be a function of basic project characteristics such as project size, project type, and facility type. It is reasonable to hypothesize that the size and/or complexity of a project will affect the IQ/OQ cost for a project. On a basic level, the total project size indicates the volume of work that will be required to complete IQ/OQ, which would then be directly related to IQ/OQ costs.

There are several potential measures of project size and complexity, including total project cost, major equipment costs, facility capacity (in terms of product count per year, etc.), or major equipment count. For this study, the total cost of engineering, materials, equipment, and construction (in other words the total installed cost – TIC)³ serves as a proxy for the project size or complexity.

Table B shows the regression relationship between the natural log of the TIC and the natural log of the IQ/OQ cost. (Regression relationships presented in this study use student’s t-test. In the tables illustrating the regression relationships, the “t-score” and “probability” (p>t) associated with each regression will be included. Both the t-score and probability

provide an indication of the statistical significance of an independent variable in the regression. For example, in Table B, the large t-score associated with $\ln(\text{TIC})$ indicates that this independent variable is a statistically significant driver of $\ln(\text{IQ/OQ cost})$, which is the dependent variable in our regression. (t-score varies with number of observations and has to be viewed in parallel with $p>t$, but generally, a rule of thumb is that if the absolute value (i.e., plus or minus) of the t-score is greater than 2.00, then the variable is a statistically significant driver.) The probability ($p>t$) also expresses the “confidence” with which a variable is regarded to be significant in the regression. The general cut-off for the analyses in this study is 90 percent confidence, or $p>t=0.10$. (i.e., there is 90 percent confidence that the correlation is not due to random chance). Note also that in cases where $p>t$ is quoted as 0.00, this does not mean it is absolutely zero, but merely that it is zero to two decimal places, or put another way, it is smaller than 0.005).

The correlation between TIC and IQ/OQ cost was found to be very strong. Figure 1 graphically shows the strength of the relationship. Clearly, TIC is the single best predictor of IQ/OQ cost. (Note that the Figure uses log scales, hence the presence of minus numbers).

Other Significant “Uncontrollable” Characteristics

After controlling for size, other characteristics were examined for their significance in “explaining” variance in IQ/OQ costs.

- **Biological Facilities.**⁴ For the facility types in the study dataset, a significant relationship was found between biological facilities and higher IQ/OQ costs. For biological facilities in the study, the average IQ/OQ cost as a percentage of TIC was twice as large as the average percentage for the other facility types.
- **Pilot Plant Facilities.** For the facility types in the study dataset, a significant relationship was found between pilot plant facilities and lower IQ/OQ costs. Although a first glance at this result suggests that pilot plant facilities may be less rigorous in their approach to IQ/OQ, hence driving lower costs, the overall data collected for this study does not support that finding. In fact, the pilot plant facilities, especially those making products to be used for clinical trial, appeared to perform the same set of qualification activities and apply the same set of quality standards as the other projects in the study database. However, the findings indicate that the qualification effort for these facilities may be smaller, if not less rigorous, relative to the total costs of equipment and materials being installed than non-pilot facilities.
- **Stand-alone Project Type.** A significant relationship was found between stand-alone facilities and higher IQ/OQ costs. As with the relationships between facility types and IQ/OQ cost, a first glance at project types suggests

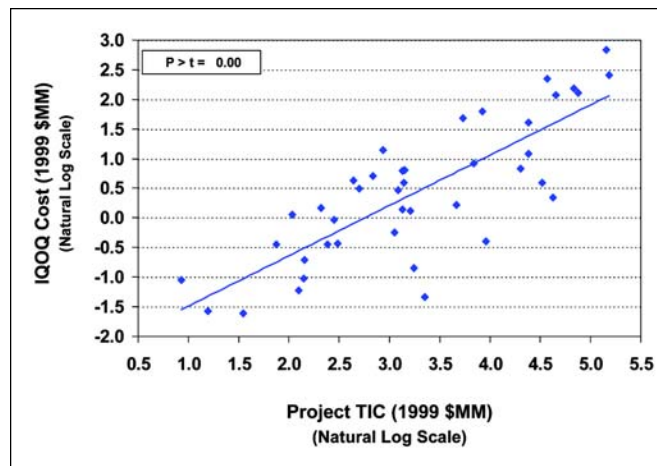


Figure 1. IQ/OQ cost is driven by facility Total Installed Cost (TIC).

that stand-alone facilities would require more expensive IQ/OQ based on the requirements to execute qualification on all new facilities, including air-handling, utility tie-ins, etc. In contrast, expansion and revamp projects, by definition, are installed in existing facilities where it is likely that certain qualification activities have been performed previously. It is interesting that the significance of the relationship between stand-alone project type and IQ/OQ cost holds up even after controlling for total project size.

For the drivers of IQ/OQ cost described above, each one is significant within a multilinear regression of all variables. Table B shows the regression relationship between the natural log of the IQ/OQ cost and the key “uncontrollable” project characteristics based on their fit within a multilinear regression analysis.

Key “Controllable” Drivers

A “controllable” driver that was found to have a major influence on IQ/OQ cost was qualification schedule definition.

- **Qualification Schedule Definition.** After controlling for project size, facility type, and project type, the following key project practice was seen as a significant driver of IQ/OQ cost: Qualification schedule definition at the time of authorization/detailed engineering start. The quality of schedule planning for the projects in the study ranged from Critical Path Method (CPM) planning to milestone schedules to schedules consisting of start and end dates only. For this analysis, the quality of the overall project schedule was broken out from the quality of the commissioning and qualification schedule. A statistically significant relationship was seen between the quality of the qualification schedule and IQ/OQ cost. For projects that had prepared a schedule to a critical-path or milestone level, IQ/OQ costs were lower than for projects that were working toward end dates only or had no schedule at all.

Even when a large portion of the variance in IQ/OQ cost is

accounted for by basic characteristics such as size, facility type, and project type (in other words, even when these characteristics are “held constant”), the quality of the qualification schedule accounts for some remaining variance in the data and is a statistically significant driver of IQ/OQ cost.

Table B shows the regression relationship between the natural log of the IQ/OQ cost and the “controllable” qualification schedule driver based on its fit within a multilinear regression analysis.

Other IQ/OQ Cost Drivers

In total, the “base” model, described by the variables above, explains approximately 80 percent of the variance in the cost of IQ/OQ for pharmaceutical projects.

Several project characteristics and practices explain some of the remaining variance in IQ/OQ cost as shown in regressions against the residual of the base model. Three of these factors are significant within a 95 percent confidence level and are described below:

- **Vendor Qualification Support.** For the purposes of this analysis, projects were classified into three categories: 1. projects for which there was no significant involvement of vendors in the qualification effort, 2. projects for which there was some vendor participation in the execution of IQ and/or OQ, 3. projects in which vendors executed entire protocols and/or delivered “prequalified” equipment or skids to the project team. The analysis shows that greater vendor involvement correlates with lower IQ/OQ cost.
- **Project Manager Assurance Team Development Issues**
- **Quality Assurance Team Development Issues.** The projects in the study were classified as to whether, during the life of the project, they experienced any “issues” with the key team members on the project. Issues include late arrival on the team, inability to participate as much as required, because of conflicting priorities, competing projects, etc., and turnover. Team issues related to the project manager and/or quality assurance representation were statistical drivers of higher IQ/OQ cost.

Three remaining practice or characteristics variables were found to correlate with IQ/OQ cost and were statistically significant within a 90 percent level of confidence when regressed against the “base” model:

- **Attendance by Qualification Personnel at Factory Acceptance Tests (FATs) and/or Site Acceptance Test (SATs).** The participation of qualification personnel corresponds with lower IQ/OQ cost.
- **Other Validation Group Requirements.** If qualification personnel had to divide their time between the qualification work on the project and a requirement to perform other tasks (such as writing Standard Operating Proce-

dures (SOPs) or batch records and/or performing technical assessments), then this was found to increase total IQ/OQ costs.

- **New Technology.** Projects containing some aspect of new technology correlate with higher IQ/OQ cost.

Other Practices that Correlate with IQ/OQ Cost Performance

Other practices that correlated with IQ/OQ cost performance included:

- **Commissioning and Qualification Integration.** For the purposes of IQ/OQ cost analysis, many of the projects could be placed in two categories:
 1. projects with no planned or executed integration of commissioning and qualification
 2. projects in which the planning and execution of qualification included referrals to commissioning tests as part of IQ and/or OQ execution

Not surprisingly, the data suggest that increased integration of activities correlates with lower IQ/OQ cost.

- **Impact Assessment.** The occurrence and formality of Impact Assessment activities correlate with lower IQ/OQ costs for the projects in this study.
- **Project Team Status.** Two issues surrounding project team status at the time of authorization correlate with IQ/OQ cost. First, projects in which there is a clear understanding of the project objectives and target dates by all members of the project team have lower costs. Second, projects in which team roles and responsibilities are defined and understood by all members of the project team also have lower IQ/OQ costs.
- **Retest.** Not surprisingly, projects noting that changes and retest were required for qualification appear to have spent more on IQ/OQ costs.
- **Approach to Automation Qualification.** Projects relying on a separate approach to Computer System Validation (CSV), that is those project teams that wrote and executed separate IQ/OQ protocols for process equipment and utilities versus automation, appear to spend more on IQ/OQ costs.

Analysis of Qualification Schedule Schedule Data Limitations

The IQ/OQ schedule represents a period of time during which resources are allocated and plans, schedules, and controls are put in place for the qualification effort. The “meaning” of the IQ/OQ duration varied somewhat from project to project. For some projects, this duration included a significant portion of

the protocol writing, review, and approval cycle; for others, it included only protocol execution and report writing. The defined start and end dates also varied slightly from project to project as the “boundary lines” between OQ and PQ were sometimes blurred. (As with the cost data collection methodology, the way this was resolved was to define what would be considered within the schedule boundaries. In this case, only protocol execution and report writing were considered in the IQ/OQ schedule. This is another example of how “messy” data was normalized across projects.) For the purposes of this study, these overlaps were essentially randomized, and while contributing to the overall variability of the cost and schedule data for these phases, they do not significantly impact the industry outcome benchmarks.

Qualification Schedule Models

There are several ways to examine qualification schedule performance of projects in the study database. As a broad analysis, the overall duration of IQ/OQ (from the start of IQ to the end of OQ) is renewed. Another means of studying qualification schedule performance is to examine the duration from the end of construction (mechanical completion) of a facility to the end of OQ.

Duration of IQ through OQ

To examine the duration of IQ/OQ (IQ/OQ schedule) the “start” of IQ can be defined as the date when the first IQ protocol is executed and the “end” of OQ as the date when the last OQ protocol is executed and/or the final OQ report is written.

An important reason to study the IQ/OQ schedule is the relationship seen between qualification cost and qualification schedule. The duration of IQ/OQ represents a period of time when resources must be allocated to the effort, including validation and quality assurance personnel, owners and contractors, and possibly plant operations and maintenance. In addition, plans, schedules, and controls must be in place for the duration of IQ/OQ. Therefore, the total IQ/OQ schedule in this analysis, was examined.

Duration of Mechanical Completion through the End of OQ

Another means of studying qualification schedule performance is to examine the duration from mechanical completion of a facility to the end of OQ (MC/OQ schedule). This is perhaps a more powerful way to consider schedule performance, as it is the best description of how much time is “lost” between the point when a facility is “ready” to make product from a mechanical basis and when it is “ready” to make product from a regulatory standpoint (of course, the completion of OQ is not actually the final step in the project process that is required for the regulatory approval to make product. Performance Qualification (PQ) often must follow and often overlaps with OQ, and all IQ, OQ, and PQ activities provide the basis for process qualification or validation. For the purposes of the analyses in this study, we will stop at the completion of OQ and examine the later stages of qualifica-

Key Drivers	t-score	P > t
Project Size: [ln(TIC)]	2.49	0.02
New Technology	-2.10	0.04
Percentage Overlap of IQ and OQ Schedules (months that IQ and OQ overlap divided by months of total IQ/OQ duration)	2.77	0.01
Engineering Definition at Authorization	2.01	0.05
Qualification Schedule Definition (CPM or milestone schedules vs. no schedule planning/end-date only)	-3.03	0.01

Table C. Relationship between key characteristics and practices and IQ/OQ schedule.

tion/validation in future studies). Therefore, the MC/OQ schedule was examined in more detail in this analysis.

As with IQ/OQ duration and IQ/OQ cost, a relationship exists between MC/OQ schedule and IQ/OQ Cost. Although it is not obvious that one outcome is driving the other, the correlation is statistically significant.

The IQ/OQ Schedule Model

As with IQ/OQ cost, IQ/OQ schedule correlates with TIC, which may be seen as a proxy for overall project size and complexity. However, the regression relationship is not as strong as that seen for IQ/OQ cost, and other drivers are found to be just as influential as size. Therefore, rather than holding a single characteristic constant, as was done with project size when examining IQ/OQ cost, project characteristics and practices can be examined directly against the IQ/OQ schedule.

Table C shows the regression relationship between the natural log of the IQ/OQ schedule [ln(IQ/OQ schedule)] and the key project characteristics and practices that make up the IQ/OQ schedule model. The statistics presented in the table are based on the fit of the independent variables within a multilinear regression analysis.

“Uncontrollable” Characteristics

- **Project Size.** Greater TIC correlates with longer IQ/OQ schedules.
- **New Technology.** For the IQ/OQ schedule analysis, projects were grouped into three categories: 1. projects containing no new technology, 2. projects containing some aspect of technology, process, or product that can be considered new to the company or site, and 3. those projects incorporating technology new to the industry. Increasing “new technology” ratings correlate with increased IQ/OQ schedules.

Key “Controllable” Drivers

- **Percentage Overlap of IQ/OQ Schedules.** Increased schedule overlap *increases* the total IQ/OQ schedule. This is a very interesting finding given that one could reasonably assume that overlapping IQ/OQ would lead to a *shorter* overall duration. In fact, overlapping all phases within a project schedule is usually done to decrease the

overall duration of the project. In the MC/OQ schedule analysis, some schedule overlaps do, indeed, drive faster schedules, but the empirical data show that this is *not* true for IQ/OQ.

The reasonable explanation for why increased overlaps drive longer IQ/OQ schedules may be derived from an examination of why overlaps “fail” to produce the desired goal (faster schedules) for any phases within a project. The primary reasons are lack of planning in turnover from one phase to the next and repeated efforts. For example, a qualification team may complete IQ for one system and then start OQ. If upon review of the executed IQ protocol an error is discovered and retest is required, this can then have a subsequent effect on OQ, requiring retest in this phase as well.

Because the correlation between percentage IQ/OQ overlap and IQ/OQ duration is so strong, project teams may want to carefully examine their strategies for overlapping schedules and be sure that controls and contingency plans are in place so that the most efficient schedules are achieved.

- Engineering Status at Authorization.** Our analyses found that as the status of engineering definition improved, the IQ/OQ duration decreased for projects in the study dataset. Earlier research has determined that Engineering Status is a critical parameter in the Front-End Loading (FEL) of projects and can be linked, along with other FEL activities, with improved absolute cost and schedule performance and predictability for pharmaceutical projects.⁵ While Engineering Status appears to be important in and of itself as a driver of qualification schedule performance, it also may be standing in as a proxy for overall early definition efforts that can impact projects throughout project execution.
- Qualification Schedule Definition.** For projects that had prepared a schedule to a critical-path or milestone level, IQ/OQ schedules were shorter than for projects that were working toward end dates only or had no schedule at all.

Other IQ/OQ Schedule Drivers

The IQ/OQ schedule variables mentioned above account for approximately 70 percent of the variance in the IQ/OQ schedules in the study database.

Other potential drivers of IQ/OQ schedule may be eliminated from the model, either because their relationship with

Drivers	t-score	P > t
New Technology	5.77	0.00
Percentage overlap of Qualification with Construction schedule	-6.76	0.00
Percentage overlap of IQ and OQ schedules	3.51	0.00

Table D. Relationship between key characteristics and drivers and MC/OQ schedule.

the dependent variable does not hold up when key characteristics are controlled or because of strong co-linearity with other, more significant schedule drivers. However, their relationship to IQ/OQ schedule is suggestive. In addition, there is some overlap with the practices that appeared significant in our cost analyses.

- Commissioning and Qualification Overlap.** As discussed for the IQ/OQ cost analysis, the data suggest that increased overlap of activities correlates with shorter IQ/OQ schedules.
- Other Validation Group Commitments.** Projects in which personnel involved in qualification activities were required to perform other tasks, such as writing plant SOPs or batch records and/or performing technical assessments were found to have longer IQ/OQ schedules.
- Overlap of Personnel Writing and Executing Protocols.** For the majority of projects in the study, the personnel responsible for writing protocols also were responsible for executing protocols. For those projects in which there was no overlap or overlaps were minimal, a correlation with longer IQ/OQ durations was seen.

The MC/OQ Schedule Model

Table D shows the regression relationship between the natural log of the MC/OQ schedule [$\ln(\text{MC/OQ Schedule})$] and the key project characteristics and drivers that make up the MC/OQ Schedule Model. The statistics presented in the table are based on the fit of the independent variables within a multilinear regression analysis.

“Uncontrollable” Characteristics

- New Technology.** As with IQ/OQ schedules, increasing “new technology” ratings correlate with longer MC/OQ schedules. Based on the regression analysis, it is clear that the extent to which projects incorporate new technology is a very strong driver of the MC/OQ duration for pharmaceutical industry projects. New technology was determined to be the only significant project characteristic in the MC/OQ Schedule Model.

Interestingly, although total project size is a driver of both IQ/OQ cost and IQ/OQ schedule, this project characteristic is not a significant driver of MC/OQ schedule in a multilinear regression model. However, total project size correlates with MC/OQ duration in a simple regression analysis.

Key “Controllable” Drivers

The following schedule overlaps were significant drivers of MC/OQ duration in the MC/OQ schedule model:

- Percentage Overlap of Qualification with Construction Schedule.** Not surprisingly, increased overlap drives *decreased* MC/OQ schedule.

The correlation between percent overlap of construc-

tion and qualification and MC/OQ duration is so strong that this appears to be a relatively simple strategy for project teams to decrease the time between when a facility is mechanically ready and when it is “ready” from a regulatory standpoint. Obviously, increased overlaps require increased coordination between construction and validation personnel in the field, as well as earlier planning, scheduling, and resource allocation. For the projects in the study database, it appears that project teams were able to prepare for and execute these overlapped phases and gain a schedule advantage.

Figure 2 shows the strength of the relationship between percentage overlap of construction and qualification and MC/OQ schedule. This schedule overlap is the strongest predictor of MC/OQ duration in the MC/OQ model. (Note that the Figure uses a log scale for MC/OQ schedule, hence the presence of minus numbers).

- **Percentage Overlap of Installation Qualification and Operational Qualification Schedule Phases.** Increased overlap drives *longer* MC/OQ schedules. This result is consistent with the relationship between IQ/OQ overlap and the overall IQ/OQ schedule.

Other MC/OQ Schedule Drivers

The above variables account for approximately 75 percent of the variance in the MC/OQ schedules in the study database.

Other potential drivers of the MC/OQ schedule may be eliminated from the model, either because their relationship with the dependent variable does not hold up when key characteristics are controlled for, or because of strong collinearity with other, more significant schedule drivers. However, we want to note these drivers, whether characteristics or practices, because their relationship to MCOQ durations is suggestive, within the limits of the database.

“Uncontrollable” Characteristics

- **Project Size.** Greater TIC correlates with longer MC/OQ schedules.
- **Process Complexity.** For this analysis, process complexity is measured by the number of steps in a process required to perform all chemical and physical operations for the manufacture of product. For projects in the study database, our analysis shows that an increased number of process steps correlates with longer MC/OQ durations. This is not an unexpected result; and it is assumed that more complex processes take longer to complete qualification requirements, especially if the qualification strategy is to use a system-by-system approach.
- **CIP/SIP.** Based on regression analysis of a categorical (1,0) variable representing projects that were required to install Cleaning-In-Place (CIP) and/or Sterilize-In-Place (SIP) systems, this project characteristic was found to correlate with increased MC/OQ duration.

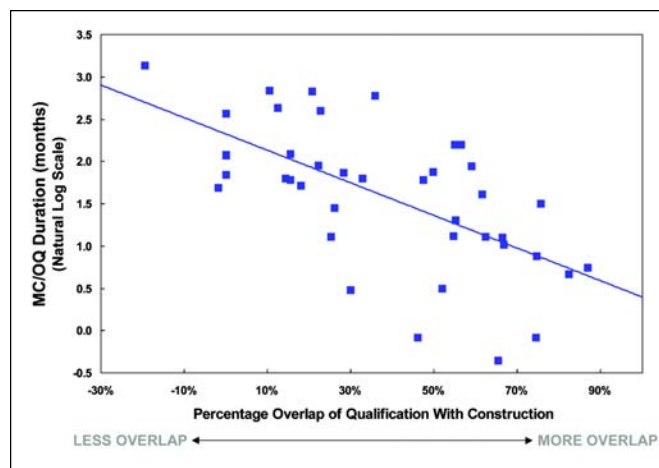


Figure 2. MC/OQ schedule is correlated with the percentage overlap of construction and qualification.

“Controllable” Drivers

- **Commissioning and Qualification Overlap.** The data suggest that increased overlap of activities correlates with shorter MC/OQ schedules. For this analysis, it was not possible to evaluate if there were schedule trade-offs between commissioning and IQ/OQ and/or MC/OQ. This may be examined in more detail in future analyses.
- **Overlap of Commissioning and Qualification Team Personnel.** In addition to the tasks required to complete commissioning and qualification, the personnel used to complete these phases varied among companies and among projects within companies. For the majority of projects, the same team was used to perform all activities under the commissioning and qualification umbrella, or there was active communication and crossover between teams. A minority of projects used different personnel to execute the activities described as commissioning versus qualification. Projects were placed into one of three categories describing the extent of team overlaps. Projects with increased overlaps of commissioning and qualification personnel achieved shorter MC/OQ durations.
- **Engineering Status at Authorization.** As described for the IQ/OQ schedule, as the status of engineering definition improved, so the MC/OQ duration decreased for projects in the study dataset.
- **Qualification Schedule Definition at the Time of Authorization/Detailed Engineering Start.** For projects that had prepared a schedule to a critical-path or milestone level, MC/OQ durations were shorter than for projects that were working toward end dates only or had no schedule at all.
- **Other Validation Group Commitments.** Projects in which personnel involved in qualification activities were required to perform other tasks such as writing plant

SOPs or batch records and/or performing technical assessments were found to have longer MC/OQ schedules.

- Existing Corporate or Site SOPs for Commissioning and Qualification.** For projects in the study database, about two-thirds were able to use existing site and corporate standard operating procedures outlining the requirements and approach for commissioning and qualification. Projects were classified as to whether the majority of activities for qualification were covered by pre-existing SOPs. The remaining projects, approximately one-third of our project sample, had either no existing SOPs, limited SOPs, or there were major changes to the existing SOPs sometime during project execution. Projects in which teams had access to existing, unchanging, standard qualification procedures, completed faster MC/OQ.
- Preparation of FAT and SAT Protocols.** The majority of projects in the study database prepared or had access to FAT and SAT protocols, which were executed as part of the project equipment procurement and construction effort.

Practice	Description
Qualification Schedule Definition at Authorization	Better-defined schedules in terms of milestone-level development or critical path analysis, resource loading, and integrated activities improve performance.
Commissioning and Qualification Overlap	Increased overlap between the Commissioning and Qualification activities is associated with improved Qualification cost and schedule performance.
IQ/OQ Overlap	Increased overlap between IQ and OQ dampens schedule performance.
Project Team Performance	Specific project team attributes are clearly associated with better performance. These attributes include avoiding key member turnover, eliminating the late assignment of key functions to the team, and avoiding multiple assignments with conflicting assignments. In addition, functionally integrated teams, well-defined project objectives, and documented roles and responsibilities improve performance.
Front-End Loading	Better-defined capital projects are clearly associated with improved absolute and predictable performance. These practices also apply to the execution of Commissioning and Qualification activities. In particular, improved Engineering Status and Project Execution Planning are important elements for Commissioning and Qualification project performance.
Existing Standard Operating Procedures (SOPs) for Commissioning and Qualification Activities	Procedures that are already in place facilitate performance. Companies without SOPs should consider developing them.
Reduce Other Validation Group Commitments	Projects with personnel who are dividing their time between activities outside of Commissioning and Qualification tasks and the Commissioning and Qualification tasks themselves, tend toward less effective Qualification performance.
Vendor Qualification Support	Vendor involvement improves Qualification costs with a neutral affect on schedules.

Table E. Qualification *best practices*.

This practice was shown to correlate with faster MC/OQ schedules and may be an indication of overall planning and controls for the projects.

- Date When the Validation Master Plan (VMP) was Finalized.** Projects were assigned into one of four categories for “sign-off” date of the VMP. VMPs were finalized and signed off at 1. project authorization, 2. before the start of construction, 3. before mechanical completion, or 4. following mechanical completion. About two-thirds of the projects were in categories two and three. The remaining projects were equally divided between categories one and four. A regression analysis of the MC/OQ duration against the date of VMP sign-off shows that projects with earlier VMP approvals demonstrate faster MC/OQ schedules. This result is not unexpected, and may be correlated with an overall level of planning for IQ/OQ execution that results in faster delivery of the qualification effort.

NOTE: The status of the VMP at the time of authorization or by the start of detailed engineering was examined for each project with the idea that the VMP may be used as a planning guide for other project definition activities and deliverables, such as cost and schedule estimates. Although it was reasonably expected that the early status of the VMP might affect later qualification outcomes, for projects in the study, VMP definition was not a significant driver of cost or schedule.

- Changing Objectives.** Projects were categorized as to whether the objectives for the project were changed during project execution. Although cost or schedule predictability outcomes are expected to be affected by these changes, which are driven from outside the project team, it is interesting to note that changing objectives also can be statistically linked with overall longer MC/OQ durations.

Conclusions

Commissioning and qualification are significant phases in the overall project delivery system. Yet surprisingly, a large number of projects systems:

- are not accurately capturing the true costs in terms of labor and currency of the qualification effort
- do not put in the effort in the early, front-end phase of a project that is necessary to sufficiently plan and define qualification activities and ensure the future success of the qualification phase

However, this study has been able to determine those planning and execution practices that are found to be statistically significant drivers of qualification success, thereby providing companies with a potential focus for their activities as they work to refine and standardize the qualification process for capital projects. In summary, those *Best Practices* are listed in Table E.

References

1. Installation Qualification is defined as: "The documented verification that all aspects of a facility, utility, or equipment, that can affect product quality, adhere to approved specifications (e.g., construction, materials), and are correctly installed." As noted in the ISPE Baseline® Guide on Commissioning and Qualification, the activities that make up IQ correspond to the inspection requirements as noted per Good Engineering Practices (GEP).

Operational Qualification is defined as: "The documented verification that all aspects of a facility, utility, or equipment, that can affect product quality, operate as intended throughout all anticipated ranges." As noted in the ISPE Baseline® Guide on Commissioning and Qualification, the activities that make up OQ correspond to the Setting-to-Work, Regulation, and Testing requirements as noted per GEP.

2. In developing the questionnaire, we would like to acknowledge the usefulness of the ISPE Baseline® Guide on Commissioning and Qualification in developing the questions. *ISPE Baseline® Pharmaceutical Engineering Guide, Volume 5 - Commissioning and Qualification*, International Society for Pharmaceutical Engineering (ISPE), First Edition, March 2001, www.ispe.org.
3. Project TIC includes design, engineering, procurement, construction costs up to mechanical completion. (In other words, it excludes commissioning, qualification, and validation costs).
4. Biological Facility – A production facility that uses cell culture (mammalian or bacterial) as the production method.
5. Lawrence, G.R., "Pharmaceutical Capital Investment: Time to Rethink Corporate Culture," *The Chemical Engineer (TCE)*, August 2004, p. 28-29.

Acknowledgements

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This article presents the new OSHA regulation regarding permissible exposure limits to hexavalent chromium, a common by-product of welding stainless steel, and how to ensure compliance. The article explains the regulation, including reasons for the stricter limit, and quotes the OSHA standard. The process for calculating the amount of fumes generated in a facility is provided, along with an example.

OSHA Limits Stainless Welding Fume Exposure to $5 \mu\text{g}/\text{m}^3$ – “What will it take to be Compliant?”

by Ed Ravert

Introduction

The term “weld fume” is a bit misleading in any discussion regarding methods to control employee exposure. The reality? Weld fume is a dust generated during the welding process making it both a dust collection and employee protection issue. Generally, the emitted fumes will be 0.6 to 7.0 percent of the welding materials used. Of this small percentage, approximately five percent would include hexavalent chromium (Cr(VI)) fumes. This article details OSHA’s new regulation¹ for employee exposure to Cr(VI) weld fume when welding stainless steel, and the most effective dust collection devices available today to meet both exposure control and air filtration guidelines.

The New Hexavalent Chromium Exposure Regulation

OSHA’s new regulation for employee exposure to hexavalent chromium, a natural metal used in the manufacture of stainless steel, has significantly reduced the permissible exposure limit from 52 to five micrograms. The regulation² also includes provisions relating to preferred methods for controlling exposure, respiratory protection, protective work clothing and equipment, hygiene, medical surveillance, hazard communication, and recordkeeping. The new rule, effective 30 May 2006, does not require the installation of engineered controls, including dust collection and air filtration equipment until 30 May 2010.

Why the Tighter Restriction?

This standard applies to all manufacturing processes where hexavalent chromium is present. These compounds are widely used in the chemical industry as ingredients, catalysts in pigments, metal plating, and chemical synthesis. And, while all types of welding could be affected, the highest concentration will be the fumes generated in welding stainless steel. The major health effects associated with exposure to Cr(VI) in-



Figure 1. Portable cartridge weld fume collector.



Figure 2. Swing arm weld fume collector.

clude lung cancer, nasal septum, ulcerations and perforations, skin ulcerations, and allergic and irritant contact dermatitis.

This new regulation provides for greater employee protection against these health risks by lowering the Permissible Exposure Limit (PEL) for hexavalent chromium, and for all Cr(VI) compounds, from 52 to a much more stringent five micrograms of Cr(VI) per cubic meter of air ($5 \mu\text{g}/\text{m}^3$) as an eight-hour time-weighted average.

Quotes from the Regulation

“OSHA concludes that engineering controls, such as Local Exhaust Ventilation (LEV), process control, and process modification or substitution can be used to control exposures in most operations.”²

“OSHA has determined that the primary controls most likely to be effective in reducing employee exposure to Cr(VI) are Local Exhaust Ventilation (LEV) and improving general dilution ventilation. ...this includes installing duct work, a type of hood, and/or a collection system.”⁴

“Paragraph (f) of the final rule, Methods of Compliance, establishes which methods must be used by employers to comply with the PEL. It requires that employers institute effective engineering and work practice controls as the primary means to reduce and maintain employee exposures to Cr(VI) to levels that are at or below the PEL ... Engineering

controls can be grouped into three main categories: 1. Substitution, 2. isolation, and 3. ventilation, both general and localized.”⁵

“**Welding:** The welding operations OSHA expects to trigger requirements under the new Cr(VI) rule are those performed on stainless steel, as well as those performed on high-chrome-content carbon steel and those performed on carbon steel in confined and enclosed spaces. ... OSHA has determined that engineering and work practice controls are available to permit the vast majority (more than 95 percent) of welding operations on carbon steel in enclosed and confined spaces to comply with a PEL of $5 \mu\text{g}/\text{m}^3$ OSHA has determined that the PEL of $5 \mu\text{g}/\text{m}^3$ also is feasible for all affected welding job categories on stainless steel. ... The two most common welding processes, Shielded Metal Arc Welding (SMAW) and Gas Metal Arc Welding (GMAW), ...may require the installation or improvement of LEV. ... There are ongoing efforts to reduce the use of SMAW and replace it with GMAW for both efficiency and health reasons. ... OSHA has revised its estimate of the percentage of SMAW welders that can switch to GMAW from 90 percent to 60 percent. ... For those stainless steel SMAW operations that cannot switch to GMAW and even some GMAW operations, the installation or improvement of LEV may be needed and can be used to reduce exposures. OSHA has found that LEV would permit most SMAW and GMAW operations to comply with a PEL of $5 \mu\text{g}/\text{m}^3$, OSHA recognizes that the supplemental use of respirators may still be necessary in some situations.”⁶

Do We Need New Dust Collection and Air Filtration Equipment? Or, Can we Retrofit Existing?

If your operation has a well designed and operating close-capture hooding system followed by a cartridge dust collector that exhausts the “cleaned” air outdoors, you should be in compliance with the new OSHA $5 \mu\text{g}/\text{m}^3$ requirement. However, if the air is returned into the work place, there should be a monitored HEPA after-filter.

Ambient air fume control systems, with a cartridge dust collector, followed by a HEPA after-filter, can be effective in removing welding fume emissions. But note that with an ambient air system, it is probable that some contaminated fumes can be pulled up past a worker’s breathing zone. If you are using other types of fume control equipment for Cr(VI) gasses, it may be necessary to replace them with cartridge collectors and HEPA after-filters.

Weld Fume Generation

To determine weld fume control needs, the first step is to calculate how much is being generated. The various types of welding processes and the type of metal being welded produce different amounts of fumes. The weight of fumes generated is a percentage of the weight of deposited metal. This percentage can be based on the length of weld electrode used or the weight of weld electrode used. Table A lists the typical ratios to determine the amount of fume generated by welding

Welding Process	Metal Type	Range Weight of Fumes/ Weight of Deposited Metal
FCAW (Flux Core)	Carbon Steel Stainless Steel	0.9 to 2.4%
SMAW	Carbon Steel	1.1 to 5.4%
SMAW	Stainless High Alloy	0.3 to 1.4%
GMAW	Carbon Steel	0.3 to 0.9%
GMAW	Stainless Steel	0.6 to 7%

Table A. Weld fume generation ratios.

process and metal type. From this, the amount of Cubic Feet of air per Minute (CFM) needed to capture and remove the fume can be determined to ensure that the proper sized dust collector is specified.

Calculation Example:

If continuously GMAW on carbon steel at the rate of 10 pounds per hour, the maximum rate of weld fume produced would be 10 pounds \times 0.009 (0.9%) or 0.09 pounds per hour. By comparison, if continuously GMAW on stainless steel at the rate of 10 pounds per hour, the maximum rate of weld fume produced would be 10 pounds \times 0.07 (0.7%) or 0.7 pounds per hour that would need to be removed by a properly sized dust collector.

Best Dust Collection Control Approach for Stainless Weld Fumes

Media filtration units, including cartridge dust collectors, are ideally suited for collection of weld fume. Depending on the welding process, source capture systems do the best job of capturing weld fume contaminants using the least amount of Cubic Feet of air per Minute (CFM). Source capture systems include hoods, ducting, an air-cleaning device, and air moving devices (fans). The air-cleaning device can include swing arm(s) and hood(s). With separate hoods and ducting, the cartridge collector is the preferred way to deal with stainless weld fumes because the weld fume is captured before it can escape into the ambient air. If ambient air collection is desired, the welder will be required to wear personal respiratory protection at all times. Even then, and if the air is to be returned into the work place, a monitored safety HEPA filter should be used.

There are many factors that can make a source capture system impractical to collect stainless weld fume. Specifically where:

- Work involves large parts and the welder has no fixed operating position, making source capture difficult to impossible.
- The welder is unable to use a hooded system. Some source capture systems may require physical positioning by the welder. If it is unlikely that the worker will perform that positioning, the system will be rendered ineffective.
- There are a large number of small weld fume producers in

a confined area.

- Overhead cranes and process obstruction make ducting installation impossible. However, properly designed unducted systems can keep the air cleaning units out of the craneways and still achieve effective results.

NOTE: While Electrostatic Precipitators (ESPs) are widely used in the collection of weld fume in carbon steel welding, *they are not* ideally suited for collecting stainless steel weld fume as their overall efficiency is less than that of media filtration collectors.

Does the New Regulation also Apply to Field Fabrication?

Yes it does, “anytime the welder is exposed to Cr(VI) fumes.” If you are doing stainless steel welding on piping, and if the welding can be done in one place where a dust collection source capture hood can be brought to the task, personal safety breathing devices would not be needed. But if a stainless weld bead is being run 20-feet down the length of pipe, and the dust collection hood cannot move with the welder, then the Cr(VI) fumes will escape to the ambient atmosphere requiring the use of a personal safety breathing device.

Should source capture be impractical for your operation, the only practical answer is for your welders to wear appropriate protection gear. Additionally, it also would be appropriate for your welders to occasionally wear a monitor to check on compliance. Contact the American Welding Society for more information on personal safety monitors and protective gear recommendations.

Dust Collection Design Considerations

To select the appropriate media filtration solution for your operation, the following considerations need to be addressed:

- size and shape of the space where welding operations are performed
- containment generation rate and the desired steady-state containment levels
- required number of ambient air changes per hour



Figure 3. Downward flow cartridge weld fume dust collector with source capture.

- existing ventilation and replacement air rates, plus all HVAC system air volumes and airflow patterns. This applies more to ambient air than with the use of source capture systems.
- airflow pattern continuity noting seasonal variations
- appropriate filtration technology to match room layout, containment generation, and designed steady state containment levels

The Only Way to Know for Sure if You Are Compliant

The reality is that it is very likely that some Cr(VI) gas emissions will be included in the fumes generated during welding stainless steel. Generally, the emitted fumes will be 0.6 to 7.0 percent of the weight of the welding materials used. Of this small percentage, approximately five percent would include Cr(VI) fumes. While OSHA does not mandate the use of personal monitors, and as effective as source capture media filtration dust collection and air filtration equipment is, the only way to know with absolute certainty in our view is to make sure your welders, and nearby workers, wear personal monitors that can indicate the Cr(VI) fume level.

References


1. Detailed information and a copy of the 287-page regulation can be found at the OSHA Web site: <http://www.osha.gov/SLTC/hexavalentchromium/index.html>.
2. (Volume 71, Number 39, 10099-10385).
3. (Volume 71, Number 39, 10334).
4. (Volume 71, Number 39, 10262).
5. (Volume 71, Number 39, 10345).
6. (Volume 71, Number 39, 10262-10263).

About the Author



With more than 30 years of experience in the ventilation industry, **Ed Ravert** is an expert at solving industrial ventilation and air pollution problems. His knowledge and experience have earned him a position as an instructor at the annual Industrial Ventilation Conferences, where he has trained more than 600 professionals on how to evaluate the

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This article introduces numerical methods to characterize particle shape and applications in the pharmaceutical industry. Basic theory and computational methods are shown, followed by a discussion of selected applications within the pharmaceutical manufacturing cycle, such as equipment selection, process safety, process standardization, and counterfeit product detection.

Numerical Methods for Particle Shape Analysis (PSA) and Applications to Pharmaceutical Manufacturing

by David A. Vetter

Currently, many facilities handling powders assume that as long as the material is chemically identical from one batch to the next, then the batches are the same. This assumption is likely derived from liquids processing where if the material is chemically identical and reasonably well mixed; all other properties are well predicted. However, for powders, nothing could be further from the truth: a concrete wall before and after being mechanically demolished has the same chemistry, but very different physical properties. The same is also true in powdered materials: graphite dust is an excellent lubricant, while diamond dust is an abrasive, yet both are pure carbon. Understanding and predicting bulk material behavior requires tools to help understand changes in individual particle properties that may affect the bulk material. Recent work in non-pharmaceutical areas has provided new tools to identify and characterize individual particles beyond 'mean particle diameter' of size classification. One such tool is Particle Shape Analysis (PSA). PSA can be particularly useful in understanding any surface area dependent property, from electrostatics to particle flow to surface chemistry effects.

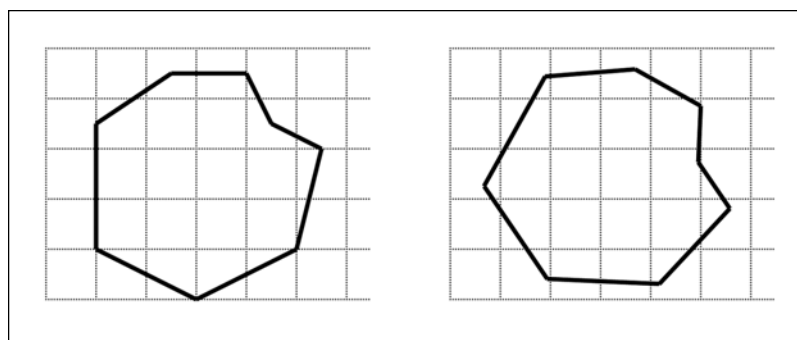
PSA has several potential applications in

pharmaceutical manufacturing. PSA is a method to measure the size, shape, and texture of particles, typically anything that can be conveniently imaged. Particles can range in size from several inches mean diameter down to smoke or soot particles. The difference between shape and texture is actually an arbitrary choice, as numeric methods show. The applications for PSA in pharmaceutical manufacturing include material property testing, quality control, material behavior prediction, and potentially detection of counterfeiting.

PSA requires an image of each particle in the sample, and a statistically large enough number of particles in a sample to be representative of the bulk material. The number of particles in a sample to be statistically valid is often surprisingly small; only 300 kernels can accurately grade a truckload of field corn. Imaging the particles can be done in either a Cartesian coordinate system (X-Y) or a polar coordinate system, and the particle must have a fairly clear definition from the background. Choice of the scanning coordinate system is entirely arbitrary, but the choice of lighting and background will aid definition. Most often, the scanning is performed using the planar coordinates with the particle resting in the

'natural' or 'lowest energy' position, i.e., the outline of the particle while it is resting on a smooth surface and not leaning against anything else. While mathematically the Fourier Transform can be used for three dimensional systems (X-Y-Z), the

Figure 1. Cartesian Coordinate System.



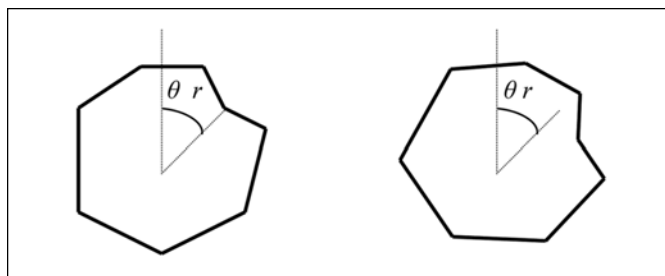


Figure 2. Polar Coordinate System.

technology to scan and interpret an object in three dimensions is not nearly as well developed as the software to manage the information after it is in the computer. (Pixar Animation is much further along at modeling three dimensional objects than most body/facial recognition software or motion capture systems are at capturing fine detail) Particle Shape Analyzers are now commercially available incorporating the microscope, a video capture device, computer, and software as a turnkey system.

Use of a Fourier Transform will make the initial particle orientation and the choice of starting coordinate system irrelevant. In *Particle Characterization in Technology*,¹ J. Beddow proposed using a Fourier transform of the scanned particle samples' coordinates as a means to quantitatively analyze particle shape. This mathematical method has several advantages in particle analysis: the computation is not difficult in terms of computer power; it is possible to automate both the particle scanning and the computation; the transformed 'values' do have some direct correlation to physical properties; the transform is independent on the starting orientation of the particle; and statistical analysis of the results becomes possible. The mathematical process of the Fourier Transform translates the series of 'perimeter' coordinates into a series of coefficients or factors.

The correlation works as follows: the first Fourier coefficient represents mean particle diameter; the second coefficient is the degree of linearity (rod like); the third coefficient is how triangular; the fourth how square the particle is, etc. As is the case with waveform building in electrical signals, a combination of coefficients can create almost any closed shape. Particles with 'higher order' coefficients (above what

might be considered 'shape') that have a relatively higher value are particles that have extended surface area and may be more reactive in any surface area dependent process such as ignition/combustion or leaching/solvation (the reverse of crystallization). Systems that J.K. Beddow and A. F. Vetter studied at length and found a very high degree of correlation between particle shape and other properties included grain (particle shape accurately measures the number of foreign particles, number of broken kernels, and moisture content) and fleet engine maintenance (a drop of oil from the crankcase can accurately predict when an engine needs an overhaul and which engine parts have excessive wear). A deeper introduction to the mathematical calculations and the concepts influencing different milling technologies on particle shape can be found at: http://www.kona.or.jp/search/20_188.pdf.

Mathematical Coordinate Systems

Figures 1 and 2 demonstrate the issues with scanning and numerically analyzing particle shape. The same particle outline is shown, but obviously a Cartesian coordinate based table will not readily show that the two outlines are the same. A Polar Coordinate system based table may give a hint that the two shapes are identical except for the rotation angle in Figure 2, but will not easily recognize small differences in size or texture. Polar coordinates will produce very different numerical values should the origin of the coordinate system not coincide with the centroid of the figure. Transforming the data into Fourier Space eliminates the information related to the particles original orientation, and converts the mean diameter into a single coefficient. Statistical analysis of the terms after the first coefficient (mean diameter) will rapidly show if the particles are similar in shape. Since crystalline solids will tend to fracture along the same faces, the particles of a solid will tend to have the same shape if processed (milled) by the same forces. This similarity in shape holds true even when the size is different (due to the nature of crystals). This is then the heart of Particle Shape Analysis.

In Figure 3, the first five terms of the Fourier Transform are shown as if each term were dominant. In a less regular shape, these terms combine the same way a more complex wave form can be built up from simpler (shorter frequency) sine waves.

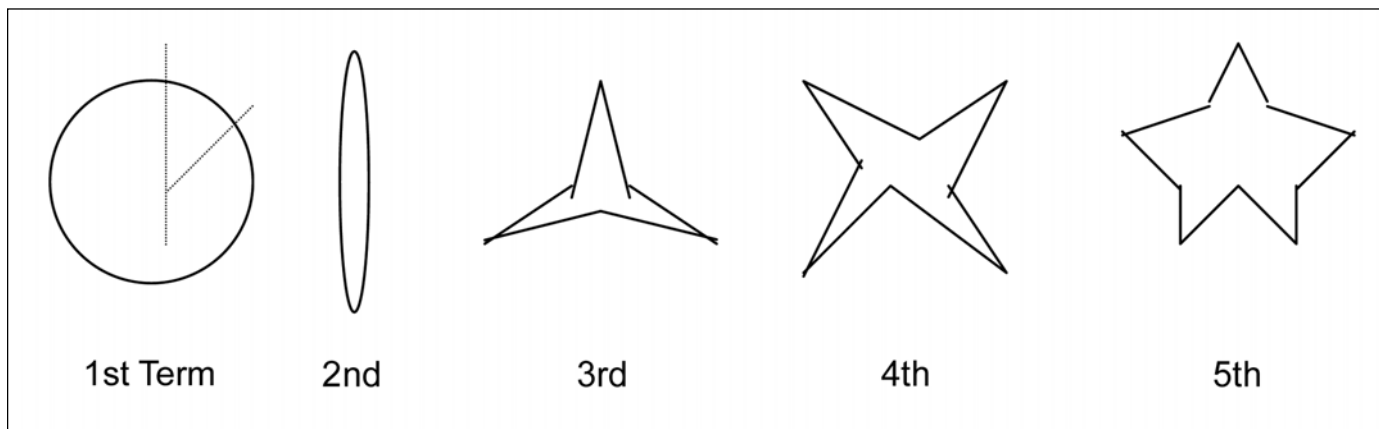


Figure 3. Examples of shapes with a dominate term among the first few Fourier Transform terms.

One limitation of the Fourier Transform should be noted: a particle shape such as Figure 4 cannot be represented in Fourier Space, as it has two separate, unconnected surface boundaries. One aspect of Fourier Space mathematics is that it can not accommodate either open figures (they must be a closed surface) or complex figures with multiple unconnected surfaces.

Finally, the choice of the initial scanning coordinate system is important if the particles are deeply convoluted such as in Figure 5. A polar coordinate system cannot resolve the particle edge when the length along angle α has multiple values. In this instance, a Cartesian coordinate scan would be preferable, but may still present issues in both normal and Fourier Space.

Process Safety

Shape or texture is a variable for dust explosions not mentioned in "Inert Milling Systems."² In "Numerical Modeling of Dust Explosions, The Influence of Particle Shape on Explosion Intensity,"³ it was shown that the particle shape or texture plays an important role in flammable dust deflagrations.

Material handling methods (including milling) of solids produce dust particles of varying shape as well as size. For potentially flammable solids, the ratio of particle surface area to mass is an important determinant of the ease of ignition and flame propagation. A particle with a high surface area to mass ratio (either small particles or a particle deviating substantially from a spherical or cubical shape) will have a much lower Minimum Ignition Energy (MIE) compared to the same chemical material, but with a larger size and/or more spherical particle shape. By analogy, if the particle size and shape resembles kindling rather than logs, the ease of starting a 'fire' changes dramatically. In pharmaceutical manufacturing, this is important in three areas: over-milling of product to a finer size than intended (process control), material property characteristics (especially if milling is near the end of the manufacturing process of the API), and choice of milling equipment.

Some of the variables in milling in food grade or pharmaceutical manufacturing are well known: desired particle size and range of acceptable particle size, power input required, process throughput rate, materials of construction relative to product hardness, dust collection, ease of cleaning between batches, etc. Safety in milling potentially flammable materials or materials degraded by heat add more complicating factors, and can prompt the use of inert gas systems.

Equipment that does not yield predictable, uniform particle size distributions from batch to batch is not under control. Variation in particle size recovery from crystallization, centrifuge, or dust collection equipment will obviously impact milling, but so will changes in starting moisture content, as well as grain size and growth during crystallization. Also critical to safety is the width of the particle size distribution: a mill that produces a higher percentage of 'fines' is more prone to ignition. A change in the filter cloth of a centrifuge leading to a higher percentage of fines before

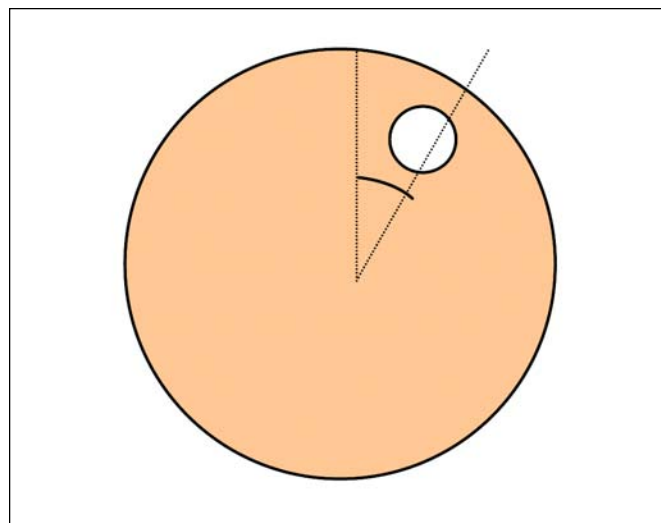


Figure 4. Example of a shape not appropriate for Fourier Transform (not a single connected surface).

milling may initially appear to be a way to increase product recovery, but not after the mill catches fire or explodes. Process control and repeatability is vital to safety in flammable material milling.

Equally critical is the shape of the particle produced by the mill: a mill that gradually abrades coarse particles (like a river producing rounded pebbles) may well produce particles with a much higher MIE than a mill that shatters particles, producing a much greater surface area. There are examples of grain milling operations that run for years without serious dust control measures and do not have dust explosions, while in one case, a mill exploded only a week after extensive changes and testing to reduce dust gave it a 'clean bill of health.' Thus, the choice of milling technology can impact process safety.

Therefore, for safety, it is imperative that the testing program² be performed on material produced by the equipment in question. Any changes in equipment OR upstream particle growth, collection, or handling processes may invali-

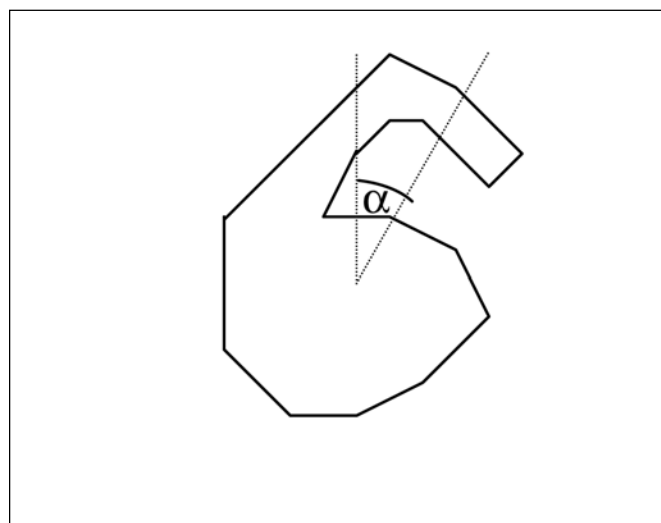


Figure 5. Example of a closed shape that is not appropriate for polar coordinates.

date the testing and lead to a false sense of security. Repeating the PSA testing from time to time to measure mill wear or unknown/unplanned process changes may be prudent for safety as well as to maintain a validated process state.

Process Control/Validation

From the process validation standpoint, changes in milling technology may represent another challenge. Changes in particle surface area of an Active Pharmaceutical Ingredient (API) could significantly change the rapidity of bio-uptake. Consider the difference of ease and speed of dissolving confectioner's sugar vs. an equal mass of sugar that has been crystallized on the walls of a container. The same amount of water and same 'power' input and time will not yield equal success in cleaning a dirty humming bird feeder as dissolving the humming bird food, despite the fact that it is 'the same material.' This is due to the fact that solvation is a surface area dependent process. Changes in particle shape/surface area may lead to changes in solution (or blood) concentration and Safety, Identity, Strength, Purity, or Quality (SISPQ) impact. There is certainly the potential for an API that is not highly soluble in the stomach (or the sterile solution for an injectable drug) to produce a substantially different end concentration in the body due to a change in particle shape, and therefore, available surface area, changing the time that it needs to dissolve. Again, particle size does not provide the complete measure of relevant material properties. See www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9090926&dopt=Abstract for a study of particle shape and in-vitro effects of the same API. In intermediate pharmaceutical manufacturing, changes in milling technology may be less troublesome than at the API stage, but can affect process cycle times. Therefore, PSA becomes a potential tool for Quality Control/Quality Assurance testing.

This also leads to using PSA to guide the choice of milling technologies. Since a significant fraction of milling in a pharmaceutical environment is near the end of API production, critical understanding all the ramifications of a proposed process change should be obvious. The normal concerns of throughput, power input, ease of cleaning, materials of construction and traceability, seal integrity, and control/capture of foreign material from mill wear will still operate. The energy input in milling will ultimately end up as heat. Products that are heat sensitive or subject to atmospheric degradation or pose a risk of flammability/explosion will likely require a mill that can be inerted. APIs may require re-validation to prove that they retain the same bioavailability after an equipment change. Easy control of sources of adulteration (either carryover batch to batch or mill wear producing unwanted metal particles) also should be testable. All of these issues are perhaps most obvious when a process moves from a clinical trial/pilot plant scale to full scale production; but relocating production to a new facility or replacing old equipment should trigger testing for both process safety/control and potential SISPQ impacts. PSA may

represent an easier method to show that a new milling technology or new equipment will not have SISPQ impact.

Unfortunately, many facilities assume that if the material is chemically the same and passes the correct screen size, their process is under control. As discussed above, there are numerous cases where this may not necessarily be true. The first improvement in control comes when the measurement includes a statistical distribution of particle sizes, rather than a simple pass/fail test of maximum particle size. Much less common and much more sophisticated is utilizing PSA and then correlating the particle shape to important parameters (such as chemical reactivity or bioavailability). For a pharmaceutical process, the correlation of particle shape to SISPQ would have to be determined material by material.

Because each material is different, understanding how a particular milling technology achieves size reduction is critical when evaluating the appropriateness of a piece of equipment for the given process application. Unfortunately, due to the potential impact of particle shape in a pharmaceutical environment, there are not many generalizations that can be safely made. Mills that shatter particles (such as hammer or cage mills) are in general more sensitive to changes in product moisture than abrasive type mills (ball mills), and require greater process control upstream of the mill to avoid unacceptable process variability downstream. Crushing (such as some roller mills) may yield more uniform particle size with fewer 'fines,' but also will produce particles with a very different shape than either 'shatter type' or 'abrasive type' mills. Even changing machine size (same manufacturer) or speeds (same machine) can have a profound impact on the product. There is simply no substitute for thorough testing and a deep understanding of the process and material properties involved. The testing must be made using the actual starting material, on the same model of mill, at the same machine speed, as the proposed equipment. The testing must also compare the range of particle sizes and a statistical measurement of shape to the existing process, be it from a clinical trial or a previous production run. Average size or percent passing a given screen size simply does not begin to provide all the relevant information.

Predicting Material Handling Behavior

With suitable testing, PSA can be used to predict bulk powder material behavior. Understanding the ratio of surface area to mass will allow predicting of how easily a dust may agglomerate, or conversely how easily it can become entrained in air. To a degree, the speed a material goes into solution can be better predicted once variability of particle surface area is controlled. PSA can explain confusing results for other surface dependent properties (such as electrostatics) when powder flow is an issue. The usual suspects for problems in particle mass flow are electrostatics and surface adhesion, due to solvent wetting (such as in a hygroscopic powder). Awareness of particle shape's influence on powder flow can add another avenue to investigate when 'bridging' in a bin is an issue.⁴ If particles have surfaces that can interlock (like a child's toy "jacks"), particle flow can be difficult and bridging

common. See also “Effect of particle shape of Active Pharmaceutical Ingredients prepared by fluidized-bed jet-milling on Cohesiveness.”⁵

Another property that PSA can easily identify is if the particles are not uniform in all three axes. Most size screening equipment is rated as withholding particles over the mean diameter of the screen openings. Note that if the particles have a high degree of rod-like or needle-like shape, they can be several times the screen opening size in length, but may still pass through the screen if the long axis happens to align perpendicular to the screen. Such particles will almost always be imaged such that the shape is evident. This kind of shape can have profound implications for electrostatics and other mass flow conditions. Another implication is if the particles are glassy (mineral) and in the 10-micron range, they may behave very much like asbestos – easily suspended in air, yet easily precipitated out in the lungs, and then difficult or impossible to excrete or be biologically modified.

Potential Detection of Counterfeit Pharmaceuticals

Theoretically, application of PSA to counterfeit detection is straightforward. Each model of mill should produce a unique ‘fingerprint’ of particle shape distributions from a particular material. Therefore, a suspect powder sample that does not match the manufacturer’s ‘equipment standard’ or shows foreign (adulterating) material would be immediately proved as counterfeit, even if the sample is chemically identical to the manufacturer’s standard. Some process changes affecting crystal growth history upstream of the mill (or potentially tableting conditions after milling) may be detectable. (Pills from different tablet presses disintegrated by the same equipment may yield different particle shapes, due to the changes in pressure, moisture content, and surface finish in the different presses). As a side benefit, the counterfeit sample may now be traceable. Should the counterfeit manufacturing location be found, PSA would become another tool to prove that this was the source of the counterfeit material (useful since many counterfeit operations may not have good enough process control to prove a counterfeiting case based on ‘chemical fingerprinting’ alone). This would be analogous to the studies by A.F. Vetter at John Deere: with statistical data from a fleet of engines any sample that deviated from the statistical norm indicated something was wrong. Usually it indicated a part in the engine was wearing abnormally, but it also inadvertently detected a mislabeled sample (wrong engine class) and on one occasion detected an aftermarket modification that had not been reported (a different/unapproved oil ring increased horsepower short term, but caused a change in cylinder wall erosion).

In each of the applications above, the first step in applying PSA is to take samples and develop a statistical norm to compare future samples against. Once the existing condition is defined, troubleshooting problems, examining the potential impact of proposed changes, or detecting deviations becomes possible.

In summation, PSA has numerous applications for process control, process safety, quality assurance, material handling troubleshooting, and potentially counterfeit detection in pharmaceutical powder operations.

References


1. Beddow, J., “Particle Characterization in Technology,” *CRC Press*, Boca Raton, Florida, 1984.
2. Jacobson, Ruby, “Inert Milling Systems,” *Pharmaceutical Engineering*, Vol. 25, No. 3, May/June 2005.
3. Ogle, R.A., Beddow, J., and Vetter, A.F., “Numerical Modeling of Dust Explosions: The Influence of Particle Shape on Explosion Intensity” Process Technical Program, International Powder Bulk Handling Process, Rosemont, Illinois 1983.
4. Stanford, M.K., DellaCorte, C., and Elyon, D., “Particle Morphology Effects on Flow Characteristics of PS304 Plasma Spray Coating Feedstock Powder Blend,” NASA, 2002.
5. “Effect of Particle Shape of Active Pharmaceutical Ingredients Prepared by Fluidized-Bed Jet-milling on Cohesiveness,” *Journal Pharmaceutical Scientists*, Vol. 94, No. 5.

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NIR spectrometry for the characterization of fuel components in a novel tamper-resistant pill bottle

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The purpose of this paper is twofold: (i) to present the Pill Safe, a novel design for a tamper-resistant prescription container, and (ii) to present use of near-infrared (NIR) spectrometry for characterization of fuel components and prediction of the burn characteristics of the fuel mixtures used to destroy tablets in the Pill Safe. In the safe, drug tablets are stacked next to fuel and attempts to force the mechanism or penetrate the bottle cause their instant destruction. The Pill Safe offers a second line of defense against the illicit distribution of dangerous prescription drugs.

Introduction

OxyContin, the brand name for the narcotic pain reliever Oxycodone-HCl (Purdue Pharma, <http://www.pharma.com/>), is categorized as a Schedule II drug under the Controlled Substances Act owing to its propensity for abuse and dependency [1]. It is an opium-based pain reliever prescribed for relief of moderate to severe pain; however, it exhibits heroin-like effects lasting up to 12 h when abused. The illicit diversion of pharmaceuticals such as OxyContin is a pervasive problem across the USA [2]. Measures have been implemented to protect pharmaceuticals and to prevent their illegal distribution. For example, electronically monitored narcotic cabinets and use of IDenticards (smart-card technology that can integrate electronic, magnetic stripe or barcode technologies, and biometric readers to increase security) have reduced diversion of drugs from hospitals and pharmacies. But it is now time for a second line of defense, in the form of well-secured, better-regulated pill dispensing

systems, to help prevent drug diversion from dispensed prescriptions. Companies have attempted to respond to this need, and e-pill (<http://www.epill.com/>) has developed a Monitored Automatic Pill Dispenser (MD.2; <http://www.epill.com/md2.html>) that features voice alarms and reminders. To our knowledge, the MD.2 is the only automated vault-like delivery system on the market. At a high retail price, the cost of dispensing new MD.2 bottles with each monthly refill would be prohibitive. Therefore, the MD.2 comes with a lock and key, and it is the responsibility of the patient to refill their bottles – potential thieves need only to obtain the key to pilfer the MD.2 contents. Thus, an opportunity lies in building an inexpensive and impenetrable container as a fail-safe, capable of scheduling and dispensing medications such as OxyContin, and deterring those interested in obtaining the drugs purely for abuse and illicit purposes.

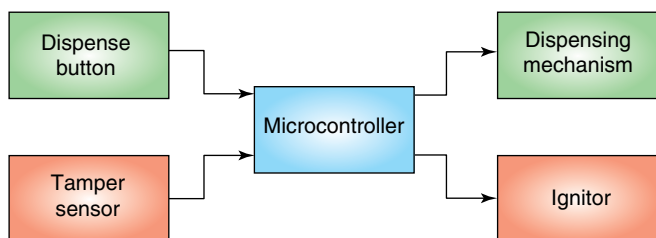


Figure 1. Schematic illustration of the main components of the medicine dispenser. A microcontroller serves as the master coordinator. Based on the inputs and programmed dispensing instructions, the microcontroller dispenses the tablet as needed. If the sensor is perturbed, the microcontroller signals for tablet neutralization, triggering the ignition of the fuel components.

Pill Safe

In response to the need for a better-protected pill bottle, the medicine dispenser presented in this research (conceived by RAMM, LLC, Bourbon County, KY USA) helps prevent the diversion of dangerous prescription drugs. The medicine dispenser simply presents the patient with a button. When

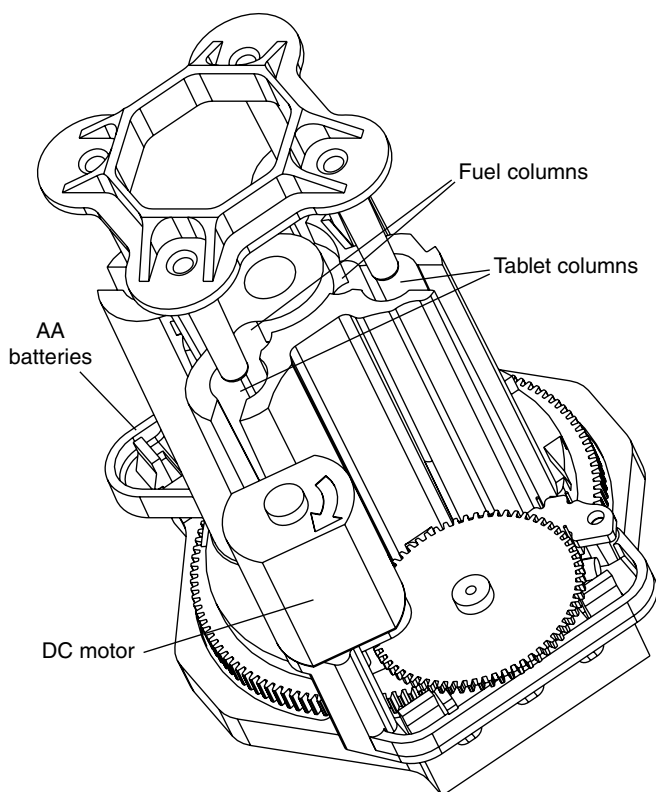


Figure 2. The medicine dispenser and its main components. Powered entirely by two AA batteries, the microcontroller activates the DC motor to dispense a tablet once per dosing period. A conductive loop wraps around the assembly. Disruption of this loop causes the microcontroller to ignite the fuel columns and incinerate the tablets. Fully assembled, the Pill Safe is 11.5 cm tall, 10 cm wide and 8.5 cm long.

pressed, it dispenses the medication through a small aperture if and only if the prescribed dosing period has passed since the previous pill was dispensed. Meanwhile, the medicine dispenser monitors its outer shell for tampering, rapidly destroying all of the pills contained within upon tamper detection. Destroying tablets rapidly requires a very fast, reliable chemical reaction that proceeds in the presence of interferences. Because the tablets are stored for an extended period in close proximity to the components of this reaction, the destructive reaction must not proceed even at a very low rate in the absence of a tampering trigger. For these reasons, a stable metallic aluminum-based fuel was chosen as the means of tablet destruction. Figure 1 gives a block diagram of the system; the mechanism shown in Figure 2 houses and delivers the pills and destroys them at the direction of the microcontroller. The pills are stored in columns adjacent to fuel. In this configuration, hot exhaust gases from the burning fuel are directed toward the pills. The entire assembly is essentially in a miniature vented Thermos® bottle, enveloped in a protective shell with a loop printed on the interior using conductive ink. Breaching the shell breaks the loop, signaling the microcontroller to ignite the fuel. The entire system is powered by two alkaline AA batteries and constructed from inexpensive parts, costing less than US \$10.

The medicine dispenser was designed to satisfy three main regulatory concerns: clinical, pharmaceutical, and packaging. From the clinical aspect, it was necessary that the burn residue from the incinerated medicine dispenser was completely destroyed and inedible. From the pharmaceutical aspect, drug tablets stacked next to fuel rods needed to be stable over time, not subject to chemical degradation in the presence of fuel. And lastly, the packaging for the medicine dispenser needed to be safe and inaccessible to those for whom the medicine is not intended. It also was designed so the hot gases created upon ignition are brief in duration and contained in an insulating vessel so there is no danger of igniting external fires.

Near-infrared (NIR) spectrometry was used in design of the fuel mixtures, for quantification of the fuel components, and for prediction of burn characteristics of the different fuel mixtures. Monitoring of fuel components using NIR is important because burn characteristics depend on the identity and quantity of fuel components (e.g., when the fuel mixture is deficient in ammonium perchlorate, the burn duration increases significantly, giving would-be thieves crucial extra seconds to break into the medicine dispenser). The fuel mixtures that were most effective in the Pill Safe were those that ignited the fastest and burned most completely. In these experiments, the concentrations were known before mixing the samples, but an in-process assay capable of assessing fuel mixtures would enable rapid and accurate detection of manufacturing and formulation inconsistencies.

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NIR has previously been used with great success for the quantification of fuel components in both solid and liquid propellant mixes [3,4]. NIR and Fourier transform infrared (FTIR) spectroscopy have been used for accurate and precise quality-control analysis of fuel pre-mixes, and have monitored antioxidant depletion over time [5]. In-process reaction information, such as intensity distribution, ignition processes, reaction temperatures, and the identity and concentrations of reaction species have been studied using the spectral range from UV and visible to NIR and mid-infrared [6]. Safety considerations for sample analysis using NIR for the study of fuel components, such as the thermal response to NIR exposure and the effects of Raman spectroscopy on the mixtures [7], also were addressed.

Theory

Absorbance in the NIR region of the electromagnetic spectrum is primarily a result of overtones and combinations of the fundamental bands from the mid-infrared and far-infrared regions. The bands are a result of anharmonic stretching and bending of functional groups such as N–H, O–H, C–H, and C=O. In most cases, the molecular structures are sufficiently complex that the spectral features of interest are highly overlapping, and thus, not directly usable without multivariate data analysis (Introduction to NIR Technology, Analytical Spectral Devices Inc., http://www.asdi.com/asd-600510_nir-introduction_rev.c.pdf). The formula for the medicine dispenser fuel source used to destroy pills included aluminum dust with iron oxide catalyst (fuel), NH₄ClO₄ (oxidizer), bisphenol A/epichlorohydrin (casting agent), and a polyamide resin (curing agent). The oxidizer, casting agent, and curing agent are the primary spectroscopically active constituents in this mixture; therefore, their concentrations were used for building and testing the regression model. Rather than using absolute mass, the prediction model used the constituent percentages (by mass) of the total mixture.

Because NIR spectra are usually a linear combination of pure component spectra, according to Beer's Law, it is theoretically possible to determine the concentration of each individual component in overlapping spectra. However, noise factors tend to complicate this procedure, such as sample inhomogeneity, particle size differences, and temperature drift. For a linear calibration model, outlying samples must be identified as outliers and removed from the calibration, or the noise and variation must be incorporated into the model. In this work, Hadi outlier detection was used to identify the spectra that belonged in the calibration model [8]. Outlier detection is generally approached by forming a clean subset of data **M** (free from outliers), followed by testing the fit of the remaining points relative to the clean subset. Consider the regression in Equation 1:

$$\mathbf{Y} = \mathbf{X}\boldsymbol{\beta} + \boldsymbol{\epsilon} \tag{Eqn 1}$$

where **Y** is an $n \times 1$ vector of responses, **X** is an $n \times k$ matrix of responses and observations, **β** is a vector of estimated regression coefficients from fitting the model to **M**, and **ε** is a matrix of errors. The best clean subset **M** is found by the deletion of the variables that result in the largest reduction in the residual sum of squares (SSE_M).

When building a calibration model from NIR spectra, it can be helpful to visualize the total instrument response, \mathbf{r}_k , as the sum of two orthogonal components: the interferences, $\mathbf{r}_k^{\bar{}}$, and the net analyte signal (NAS), \mathbf{r}_k^{\perp} , according to Equation 2 [9]. The superscript ‘ $\bar{}$ ’ denotes the fact that the interferences span the space occupied by the analyte, and the ‘ \perp ’ denotes the fact that the NAS is orthogonal to the interfering species.

$$\mathbf{r}_k = \mathbf{r}_k^{\bar{}} + \mathbf{r}_k^{\perp} \tag{Eqn 2}$$

A linear combination of the interferences produces $\mathbf{r}_k^{\bar{}}$; therefore, the signal orthogonal to $\mathbf{r}_k^{\bar{}}$ belongs exclusively to the analyte of interest [10]. A projection matrix is calculated according to Equation 3:

$$\mathbf{P}_k^{\perp} = (\mathbf{I} - \mathbf{R}_{-k}\mathbf{R}_{-k}^{+}) \tag{Eqn 3}$$

where **R**_{-k} is a matrix of samples without the analyte, **I** is the identity matrix, and the superscript ‘+’ is the Moore–Penrose pseudoinverse. The NAS vector, \mathbf{r}_{cal}^{\perp} , can be calculated from a calibration spectrum, \mathbf{r}_{cal} , by projection of the spectrum onto the null space of the rows of **R** with Equation 4:

$$\mathbf{r}_{cal}^{\perp} = \mathbf{P}_k^{\perp}\mathbf{r}_{cal} \tag{Eqn 4}$$

The NAS vector is normalized to length one by Equation 5:

$$\mathbf{r}_k^{NAS} = \frac{\mathbf{r}_{cal}^{\perp}}{\|\mathbf{r}_{cal}^{\perp}\|} \tag{Eqn 5}$$

A linear regression is fit to this vector, and the regression coefficients are used for subsequent predictions.

One advantage of using the NAS approach is in the calculation of so-called figures of merit. In severely overlapping spectra, it has historically been difficult to quantify selectivity, sensitivity, and signal-to-noise (S/N) ratio because of the inability to distinguish between interferences and the analyte of interest [10,11]. With the NAS, these quantities can be measured directly. Selectivity can be calculated as the scalar degree of overlap, α , between the NAS vector and the calibration spectrum according to Equation 6:

$$\alpha = \frac{\|\mathbf{r}_{cal}^\perp\|}{\|\mathbf{r}_{cal}\|} \quad (\text{Eqn 6})$$

The selectivity is a measure from 0 to 1 indicating how unique the analyte of interest is compared with the interferences. The sensitivity is a measure of how much the analyte varies in response to a change in concentration. This quantity can be expressed as Equation 7:

$$\mathbf{s}_k = \mathbf{r}_k^{NAS} / c_k \quad (\text{Eqn 7})$$

where c_k is the concentration of the k -th analyte. Theoretically, sensitivity should be the same for each concentration and each NAS vector [12]. The S/N ratio can be expressed as Equation 8:

$$S/N = \frac{c_k \|\mathbf{r}_k^{NAS}\|}{\|\boldsymbol{\epsilon}\|} \quad (\text{Eqn 8})$$

where $\boldsymbol{\epsilon}$ is the random instrumental error.

To prove that the relationship between NIR spectra and the fuel components is not a product of correlated initial constituent concentrations, the mixture concentrations were calculated by the following orthogonalization procedure. A random matrix \mathbf{A} corresponding to I mixtures and J components per mixture was constructed with a random-number generator. Singular value decomposition of \mathbf{A} according to Equation 9 yields orthogonal principal component scores, \mathbf{U} , between -1 and $+1$; \mathbf{S} is a diagonal matrix of singular values and \mathbf{V} is the matrix of eigenvectors (loadings) [13].

$$\mathbf{A} = \mathbf{USV} \quad (\text{Eqn 9})$$

A coefficient matrix, \mathbf{K} , was constructed according to Equation 10 such that each row contains 0 and 1.

$$\mathbf{K} = \frac{\min[\mathbf{U}_i] + [\mathbf{U}_i]_{j=1}^j}{\max[\mathbf{U}_i]} \quad (\text{Eqn 10})$$

A final matrix of concentrations was constructed by multiplication of \mathbf{K} with the fuel ratios from the accepted fuel formula [16% Atomized aluminum powder (fuel), 69.8% ammonium perchlorate (oxidizer), 0.2% iron oxide powder (catalyst), 12% binder, and 2% epoxy curing agent; http://www.nasa.gov/returntoflight/system/system_SRB.html].

In a search for the most descriptive multivariate model to correlate NIR spectra to constituent concentrations and burn characteristics, the present research compared NAS regression with principal component regression (PCR) [14], interval PCR (iPCR), and PCR-uninformative variable elimination (PCR-UVE) [15,16]. For each of these models, principal components were calculated by a singular value decomposition of the raw spectra according to Equation 9.

The regression of \mathbf{U} in Equation 11 indicates which of the components have the strongest correlation to a change in constituent concentration \mathbf{c} , where \mathbf{a} is the y -intercept, \mathbf{b} is a vector of regression coefficients, and $\boldsymbol{\epsilon}$ is the residual.

$$\mathbf{c} = \mathbf{a} + \mathbf{bU} + \boldsymbol{\epsilon} \quad (\text{Eqn 11})$$

Equation 12 demonstrates how a leave-one-out cross validation was used to predict the concentration of fuel components, where σ^2 is the variance, $f_i(\mathbf{U}_i)$ is the prediction of the model for the i -th pattern m in the training set, after it has been trained on the $m-1$ other patterns.

$$\sigma_{LOO}^2 = \frac{1}{m} \sum_{i=1}^{i=m} (\mathbf{c}_i - f_i(\mathbf{U}_i))^2 \quad (\text{Eqn 12})$$

Mixture	Al (%)	NH ₄ ClO ₄ (%)	Fe ₂ O ₃ (%)	Epoxy resin (%)	Curing agent (%)	Ignition time(s)	Burn duration(s)
1	13.34	58.03	0.37	21.46	6.81	2.0	14.0
2	10.02	60.52	0.40	21.09	7.97	1.5	11.0
3	16.69	60.47	0.51	16.96	5.36	2.0	15.0
4	9.40	69.57	0.33	15.46	5.24	0.5	9.0
5	19.23	51.70	0.55	21.53	7.00	4.0	18.0
6	17.07	44.82	0.45	28.06	9.59	3.5	26.0
7	21.33	36.64	0.39	31.31	10.33	4.0	40.0
8	13.13	56.60	0.24	22.89	7.14	2.0	16.0
9	16.65	69.92	0.27	9.83	3.33	1.0	6.0
10	12.38	63.17	0.29	18.22	5.93	1.5	12.0
11	11.02	59.31	0.41	20.06	9.2	1.5	4.0

Table 1. Constituent percentages, ignition time, and burn duration for each fuel mixture.

Continued on page 58.

NIR performance	NH ₄ ClO ₄		Epoxy resin		Curing agent		Ignition time		Burn duration	
	iPCR	NAS	iPCR	NAS	iPCR	NAS	iPCR	NAS	iPCR	NAS
r ²	0.992	0.983	0.969	0.997	0.987	0.996	0.959	0.993	0.917	0.989
RMSECV (%)	2.58	4.54	4.33	2.31	2.94	4.27	5.93	2.20	6.98	2.60
Position (nm) ^b	1566–1966		1324–1724		1633–2033		1750–2150		2088–2488	

^aNIR performance as values of r² and root-mean-square error of cross-validation (RMSECV) were predicted using interval principal component regression (iPCR) and net analyte signal (NAS).

^bThe wavelength regions were selected and used with iPCR, whereas NAS used the full spectrum.

Table 2. Predicted results for NH₄ClO₄, epoxy resin, curing agent, ignition times, and burn durations.^a

In the case of a two-component system, it is a simple matter to observe a linear change in the analyte concentration. In the presence of two system components, theoretically, the concentration change can be modeled by one principal component. The loading corresponding to this principal component accurately reflects the contribution of each wavelength to the overall classification. However, when multiple system components change simultaneously, multiple principal components are needed for the prediction model.

Interval PCR performs in similar way to the aforementioned analysis, but rather than using the full spectrum, it uses smaller subsets of variables [16]. For example, when the experimenter specifies an interval (I_n) of 100 wavelengths, the algorithm performs PCR followed by principal component selection and cross-validation on intervals of 100. With a moving boxcar, all wavelengths are paired with all other wavelengths inside of ±I_n. For example, after the algorithm analyzes 2101–2200 nm, the next iteration analyzes 2102–2201 nm, and so on. At the final wavelength, the first I_n wavelengths are added to the end for the final iterations. In this manner, each wavelength is included in a new model 2 × I_n times. The goal of interval selection is the minimization of the standard error of performance in Equation 13,

which indicates the interval with the highest correlation to the change in drug concentration:

$$SEP = \frac{\left(\frac{\epsilon^2}{N - 1} \right)^{1/2}}{\max(\mathbf{c}) - \min(\mathbf{c})} \quad (\text{Eqn 13})$$

where ϵ is the residual, N is the number of spectra, and \mathbf{c} is a concentration vector.

Experimental methods

Fuel preparation

Eleven different mixtures of ammonium perchlorate (NH₄ClO₄), aluminum dust (Al), iron oxide (Fe₂O₃), casting resin (Bisphenol A/Epichlorohydrin), and polyamide curing agent (Versamid 140; Firefox Enterprises, <http://www.firefox-fx.com/>) were constructed such that the percentage of each component did not correlate with those of the other components. Of the 11 fuel mixtures used, NH₄ClO₄ was 36.64 to 69.92% of the total mixture weight, Al was 9.40 to 21.33%, Fe₂O₃ was 0.24 to 0.51%, casting resin was 9.83 to 31.31%, and curing agent was 3.33 to 10.33%. Con-

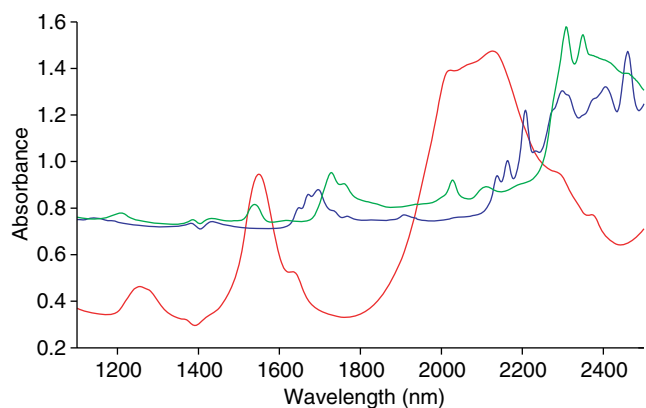


Figure 3. Pure-component NIR spectra. The spectrum for epoxy resin is in blue, that for curing agent is in green, and that for NH₄ClO₄ is in red.

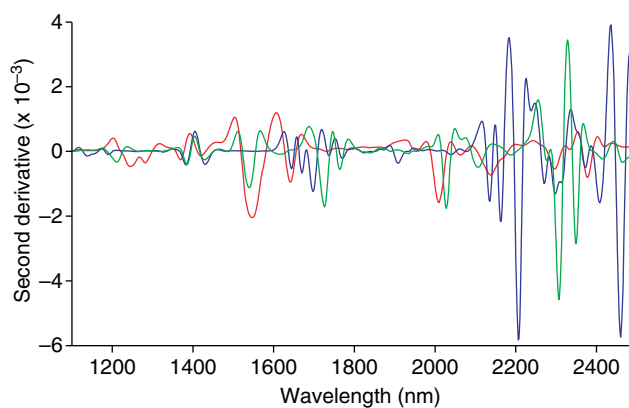


Figure 4. Second-derivative NIR spectra. The spectrum for epoxy resin is in blue, that for curing agent is in green, and that for NH₄ClO₄ is in red.

stituent ratios are reported in Table 1. Epoxy resin and curing agent were heated to 35°C on a hot plate. Powders were mixed together and stirred to ensure a homogenous mixture. Epoxy resin and curing agents were then added to the powder mixtures and stirred vigorously for three minutes. The resulting fuel was poured into a ceramic mold so it could easily be inserted into the medicine dispenser prototype.

NIR data collection

NIR spectra were collected in reflectance mode from 1100 to 2500 nm in 2 nm steps using a customized scanning spectrometer, as described previously [17]. To eliminate room noise, samples were scanned inside the instrument drawer. Each of the mixtures was scanned six times, all in random order to eliminate the effects of drift. All NIR data were exported to Matlab 7.0.1 (The Mathworks Company, <http://www.mathworks.com/>) for processing and analysis.

Ignition tests

To identify the burn characteristics, fuel samples were ignited quickly using a propane torch. With the torch and samples positioned reproducibly, ignitions were recorded on digital video and ignition start times and durations were noted (Table 1).

Analysis of NIR spectra

Algorithms for NAS, Hadi outlier detection, PCR, and iPCR were all written by the authors for Matlab 7.0.1. NAS, PCR, and iPCR were all used to predict the concentrations of each fuel component from the collected NIR spectra. These methods enabled the identification of the statistically significant regions of the NIR spectrum for the measurement of each component. Using the same methods, NIR spectra were then used to predict the ignition times and burn durations. The two most effective methods for calibration and prediction of burn characteristics were iPCR and NAS.

Extent of incineration

The extent of OxyContin incineration was determined by high-performance liquid chromatography (HPLC). The pill bottle was loaded with fuel mixture number 1 (Table 1). Burn residue from the pill bottle stacked with 20 mg OxyContin tablets (Purdue Pharma, <http://www.pharma.com/>) was ground with a mortar and pestle, washed with 200 ml of mobile phase, filtered twice through a 0.2 µm filter, and a chromatogram was collected to measure the remaining concentration of OxyContin. The HPLC assay was conducted using a Waters 717plus Autosampler, Waters 1525 Pump, and Waters 2487 Dual Wavelength Absorbance Detector with Waters Breeze v3.30 Software (<http://www.waters.com/>).

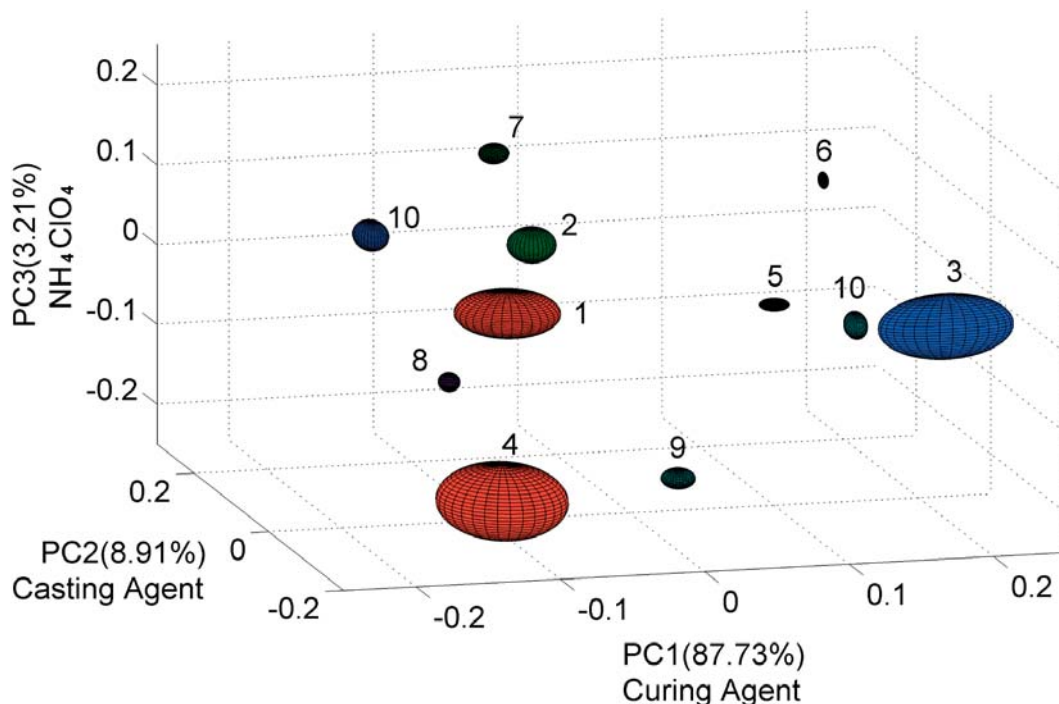


Figure 5. A plot of principal component (PC) scores indicates whether a mixture is deficient in a particular fuel component. PC score 1 correlates very highly with the presence of curing agent, PC2 with the presence of epoxy resin, and PC3 with the presence of NH_4ClO_4 . The mixture with ideal burn (fastest ignition and longest burn) was mixture number 1; therefore, projection of PC scores onto this plot can be used as a map for the prediction of fuel burn characteristics.

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A Waters μ Bondapak C18 column (300×3.9 mm) was used with the UV/VIS Detector set at a wavelength of 206 nm for OxyContin standards. The mobile phase used for OxyContin was 0.005 M 1-hexanesulfonate, methanol, phosphoric acid, and triethylamine (900:100:5:2). The flow rate of the mobile phase was at 1.5 ml min^{-1} with 10 ml injections of the sample. Standards analyzed exhibited excellent linearity over the concentration range employed. The retention time for OxyContin was 22.22 ± 0.211 min. The sensitivity of the assay was 25 ng ml^{-1} .

Results and discussion

HPLC analysis indicated that following tablet incineration using the most effective fuel mixture, the burn residue contained 5.58% by mass of the initial OxyContin. It must be noted that this 5.58% was recovered only by grinding, washing, extracting, filtering, purifying, and chromatographically separating the burn residue. With such an extensive extraction procedure and such a small yield, it is likely that would-be thieves would be sufficiently discouraged from a recovery attempt. The best fuel mixture required ~ 14 s to consume the contents of the safe completely, making it nearly impossible to break into the bottle and remove the contents before the burn was complete. The medicine dispenser is designed so that the flame is contained, and there is no danger of igniting external fires. The fuel formula contains an oxidizer; therefore, there is no need for atmospheric oxygen to sustain the reaction that destroys the tablets.

The most effective chemometric methods for the measurement of fuel components and prediction of ignition characteristics from the NIR spectra were NAS regression and iPCR. The fuel components had no significant correlation to each other; therefore, the predictive ability of the NIR was not a product of correlated concentrations. Additionally, the NAS was able to detect the portion of the signal that was unique to the analyte of interest; thus, there were two measures of certainty that the strong correlation was not an artifact. Using NAS, the NIR measurements over the respective concentration ranges resulted in $r^2 = 0.983$ and root-mean-square error of cross-validation (RMSECV) = 4.54% for NH_4ClO_4 , $r^2 = 0.997$ and RMSECV = 2.31% for the epoxy resin, and $r^2 = 0.996$ and RMSECV = 4.27% for the curing agent. NAS predicted ignition times with $r^2 = 0.993$ and RMSECV = 2.20% and burn durations with $r^2 = 0.989$ and RMSECV = 2.60%. Because this experiment was performed using cross validation, no external validation set was used. Consequently, all spectra satisfied the Hadi criterion for class membership; therefore, no spectra were discarded as outliers in the NAS calibration. The NAS calibration and figures of merit were calculated from the unsmoothed, unprocessed full spectrum data. Interval PCR data performed comparably to NAS data for the measurement of fuel concentrations, but not as well for the prediction of burn char-

acteristics. See Table 2 for comparison of iPCR and NAS performance statistics.

Pure-component and second-derivative NIR spectra from NH_4ClO_4 , epoxy resin, and curing agent are shown in Figures 3 and 4. It is apparent from these figures that the spectra were sufficiently distinct from each other, making it relatively easy to identify the NAS for each component. Iron oxide and aluminum had no distinguishing spectral features in the NIR; therefore, they were not quantified in this experiment. Of course, other fuel formulas could be used. A mixture with five components, each with its own unique NIR chromophore, might make the most sense from a quality-control standpoint. However, iron oxide can be determined in mixtures of aluminum dust using visible light spectrometry. Many NIR spectrometers are capable of collecting visible and NIR spectra simultaneously.

The figures of merit calculated from the NAS vector resulted in: selectivity = 0.014, sensitivity = 5.874, and S/N = 39.941 for NH_4ClO_4 ; selectivity = 0.005, sensitivity = 6.467, and S/N = 50.76 for the casting agent; and selectivity = 0.022, sensitivity = 4.097, and S/N = 35.32 for the curing agent. Selectivity is a unitless quantity, and sensitivity is given in units of signal per concentration. The limit of detection (LOD) is defined as the concentration at which S/N = 3 [10]. The S/N ratios were calculated separately for each individual concentration, and the theoretical LOD was extrapolated from the linear plot of concentration versus S/N. The LOD was 0.93% for NH_4ClO_4 , 1.37% for casting agent, and 1.36% for curing agent. Precision was measured by calculating the relative standard deviation (RSD) of the predicted concentrations from the NAS vector. The RSD was 0.38% for NH_4ClO_4 , 0.32% for casting agent and 0.70% for curing agent. Bias was calculated by subtraction of the measured NIR values from the reference gravimetric values. Although some of the individual measurements were offset slightly high or slightly low, there was no net bias for the calibration.

Figure 5 is a plot of principal component ellipses calculated from the fuel mixtures, demonstrating how well NIR was able to separate them. Ellipses are drawn six standard deviations from their cluster centers. NH_4ClO_4 demonstrated a high correlation to both ignition time and burn duration, suggesting that it was largely responsible for the reaction rates. High correlations were demonstrated by principal component (PC1) to the concentration of curing agent, PC2 to the concentration of casting agent, and PC3 to concentration of NH_4ClO_4 . Mixture 1 demonstrated the best burn characteristics for the purpose of this research (i.e., fastest ignition and longest burn). The cluster location from mixture 1 can quickly be compared with other fuel mixtures, enabling this figure to act as a map to identify components in which a particular mixture might be deficient. This figure also can be used to predict the ignition time and burn duration of each mixture depending on its constituent concentrations.

NIR spectroscopy is a versatile, nondestructive, and rapid method of analysis. It has been applied to both liquid and solid propellants with no sample preparation required [3–6]. As is evident from the PC clusters in Figure 5, it is also highly reproducible. Even when samples are very close to each other in concentration, they still cluster in distinctly different regions of a PC plot. This effect can be quantified by the bootstrap error-adjusted single-sample technique (BEST) [16]. According to the BEST, multidimensional standard deviations (MSD) greater than three indicate that clusters belong to different populations. When MSDs are less than three, clusters are considered inseparable. The average MSD separation between fuel mixtures was 431.36, and the average MSD separation calculated between repeat scans of the same mixture was 1.69, demonstrating the high degree of reproducibility from scan to scan. NIR analysis is also a rapid technique. NIR spectrometers can now collect thousands of spectra per second with high resolution [18], and NIR can effectively function as an in-process assay for the quantification of fuel mixtures as they are cast into the medicine dispenser model. From the 200 NIR spectra collected for this experiment, there were no aberrant scans, demonstrating that NIR is also a robust assay.


Conclusion

This research presents a novel design for a medicine dispenser, intended to provide a second line of defense against the diversion of prescription drugs. NIR spectroscopy was able to quantify rapidly and accurately the fuel components in solid fuel mixtures, and to identify burn characteristics of the different mixtures. This research suggests that Pill Safe manufacturing and the fuel analysis need not be too challenging or expensive, making it a valuable product for use in the pharmaceutical industry.

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References

1. National Drug Intelligence Center (2002) *Information Brief: Prescription Drug Abuse and Youth*. (<http://www.usdoj.gov/ndic/pubs1/1765>).
2. The New York Times (2004) Pill thefts alter the look of rural drugstores. *The New York Times* (<http://query.nytimes.com/gst/health/article-page.html?res=9C03E1D6163BF935A35754C0A9629C8B63>).
3. Wang, J. *et al.* (2004) Application of near infrared spectroscopy in liquid propellant analysis. *Huaxue Tongbao* 67, w023/1–w023/4.
4. Judge, M.D. (2004) The application of near-infrared spectroscopy for the quality control analysis of rocket propellant fuel pre-mixes. *Talanta* 62, 675–679.
5. Rohe, T. *et al.* (1996) Near infrared-transmission spectroscopy on propellants and explosives. *Int. Annu. Conf. ICT* 27, 85.1–85.10 (<http://www.ict.fraunhofer.de/english/events/anconf/a27general.html>).
6. Weiser, V. and Eisenreich, N. (2005) Fast emission spectroscopy for a better understanding of pyrotechnic combustion behavior. *Propellants Explos. Pyrotech.* 30, 67–78.
7. Harvey, S.D. *et al.* (2003) Safety considerations for sample analysis using a near-infrared (785 nm) Raman laser source. *App. Spec.* 57, 580–587.
8. Hadi, A.S. and Simonoff, J.S. (1993) Procedures for the identification of multiple outliers in linear models. *J. Am. Stat. Assoc.* 88, 1264–1272.
9. Boelens, H.F. *et al.* (2004) Performance optimization of spectroscopic process analyzers. *Anal. Chem.* 76, 2656–2663.
10. Lorber, A. (1986) Error Propagation and figures of merit for quantification by solving matrix equations. *Anal. Chem.* 58, 1167–1172.
11. Booksh, K.S. and Kowalski, B.R. (1994) Theory of analytical chemistry. *Anal. Chem.* 66, 782a–791a.
12. Lorber, A. *et al.* (1997) Net analyte signal calculation in multivariate calibration. *Anal. Chem.* 69, 1620–1626.
13. Jolliffe, I.T. (2002) *Principal Component Analysis*. Springer.
14. Leardi, R. and Norgaard, L. (2004) Sequential application of backward interval partial least squares and genetic algorithms for the selection of relevant spectra regions. *J. Chemometr.* 18, 486–497.
15. Noord, O.E. (1996) Elimination of uninformative variables for multivariate calibration. *Anal. Chem.* 68, 3851–3858.
16. Lodder, R.A. and Hieftje, G. (1988) Detection of subpopulations in near-infrared reflectance analysis. *App Spec.* 42, 1500–1512.
17. Yokel, R.A., *et al.* (2005) ²⁶Al-containing acidic and basic sodium aluminum phosphate preparation and use in studies of oral aluminum bioavailability from foods utilizing ²⁶Al as an aluminum tracer. *Nucl. Instrum. Methods Phys. Res. B* 229, 471–478.
18. Klahn, T. *et al.* (2004) A high speed NIR-spectroscopy to investigate ignition and combustion of propellants and pyrotechnics. *Int. Annu. Conf. ICT* 35, 161/1–161/9 (http://www.ict.fraunhofer.de/english/presse/anre2004_05.pdf). 

This article reviews the considerations involved in the selection of appropriate technologies for aseptic processing. It compares and contrasts conventional cleanroom operations, Restricted Access Barrier Systems (RABS), and isolation technology with respect to the advantages/disadvantages of each for use in aseptic filling. It evaluates all aspects of the selection process, beginning with project time lines, facility concerns, operation, and compliance.

Choosing Technologies for Aseptic Filling: "Back to the Future, Forward to the Past?"

by James Agalloco, James Akers, and Russell Madsen

Introduction

Designing a facility for the aseptic production of sterile products in their final containers involves consideration of many different factors. Unlike some non-sterile product or active pharmaceutical ingredient facilities that can sometimes be adapted for the production of different products, parenteral facilities can be difficult to modify to fit changing circumstances. The choices made regarding facility arrangement, HVAC system, and equipment selection during initial facility design can only be altered at considerable expense with significant downtime once the facility has been placed in operation. To ensure success, it is essential that the design meet specified operational requirements and constantly evolving regulatory expectations. It is important to consider that a firm may be living with initial design decisions for a long time since the useful lifetime of a facility may exceed 15 years. With the introduction of new aseptic processing technologies over the last decade, those designing and constructing aseptic processing facilities are now faced with several technology alternatives.

This article will focus on which environmental technology affords the best facility design choice considering production utility, flexibility, and longevity in the rapidly evolving aseptic processing landscape. Among the contamination control design alternatives that can be considered are:

- Conventional cleanroom facilities with various types of barriers (rigid or flexible)¹
- Restricted Access Barrier Systems (RABS)²
- Isolators (closed or open)³

In recently reviewed projects, firms have considered elements of all three of the alternatives listed above. For example, sterile compounding may be done in isolators, while filling may be done in a conventional cleanroom using some variety of barrier technology. Modern sterile products facilities are typically outfitted with equipment that includes barriers of one type or another. Additionally, modern aseptic processing equipment can include a substantial amount of automation that may accomplish the same objective as barrier systems: the reduction of potential risk from human-borne contamination.

There are other production technologies available (i.e., blow-fill-seal, closed-vial filling), but these do not provide the means to fill the full range of product formulations or container presentations.^{4,5} Their selection, while offering substantial advantages, may restrict their application to special circumstances. In the case of blow-fill-seal, the equipment contains its own air handling system and the need for human intervention is restricted by design. Environmental considerations for closed vial filling are still under discussion. The core facility technologies listed above are commonly selected since they offer the greatest flexibility in use over what is expected to be a lengthy operational life.

A general description of the more prevalent environments for aseptic processing is useful to understand the unique elements of each. Each of these incorporates "state-of-the-art" elements as would be found in a new facility designed for high-throughput aseptic filling. The focus of the descriptions is on the filling environment, as the formulation areas for each would likely be essentially identical.

Conventional Facility

The core of the aseptic area is curtained or partitioned-off to define the aseptic processing area in which ISO 5 (traditional FED-STD 209E Class 100 unidirectional air flow) conditions are specified.^{6,7} Surrounding this is an environment of slightly lower class, often ISO 6 or 7 (Class 1,000 to 10,000) in which the personnel work the majority of the time that they are in the aseptic processing area. EU expectations are for the ISO 5 unidirectional airflow aseptic filling environment to be accessed from an ISO 5 background environment (when classified under static conditions) in which unidirectional flow is not required.⁸ Several firms have addressed this by designing a background environment that meets ISO 5 under dynamic conditions by providing unidirectional air supply throughout the filling room. Other facility designs have succeeded with ISO 6 or 7 both of which can be compatible with EU Grade B requirements depending upon how classification is accomplished. Sterilizers are unloaded in this area, and personnel transfer sterilized items to the ISO 5 environment. Glass containers are typically fed directly to the aseptic processing environment using continuous-feed dry-heat tunnels. Sanitization of the facility using a defined disinfection program is performed at routinely scheduled intervals to meet current regulatory and cleanroom practice expectations. Personnel working in the aseptic area wear sterilized garments over their entire bodies to minimize the release of contaminants. Operators access the ISO 5 environment using gloved hands and frequently some part of the gown also will enter this critical zone. The human activities conducted in ISO 5 environments are those required to perform the set-up, environmental monitoring, and routine and non-routine interventions.

RABS Facility

The core of the aseptic area includes an isolator-like structure that defines the ISO 5 aseptic processing area in which unidirectional airflow conditions are generally specified. Surrounding this is an ISO 6 or 7 environment in which the personnel are located during work. Full adherence to EU expectations would mandate a "Grade B" (which is ISO 7 under dynamic conditions or ISO 5 at rest) background environment as described for cleanrooms (see Conventional Facility above). Sterilizers are unloaded in this area and personnel transfer sterile items into the ISO 5 environment using Rapid Transfer Port (RTP) systems or transfer hatches.⁹ Containers are fed directly to the ISO 5 environment using continuous-feed tunnels. Sanitization of the facility and RABS internal surfaces using a defined disinfection program is performed on a routine basis to maintain control over microbial contamination. An environmental monitoring program, confirming the microbial and non-viable particle conditions meet the desired state, is required for the RABS and the surrounding room. Personnel working in the aseptic area wear sterilized garments over their entire bodies to minimize the release of contaminants. The operators use gloves on the RABS in conjunction with the RTP to perform set-up, environmental monitoring, and any required interventions.

Because of the need for flexibility or due to product considerations it may be necessary to allow gowned operator access without the use of RABS features. Thus, RABS could operate in at least two different states of control, one in which there are no direct interventions and another in which direct, open-door interventions are permitted in the same manner as in a conventional cleanroom. In the latter instance, the user would place restrictions on the frequency with which a door could be opened and define the circumstances of the interventions. Operated in that manner, the RABS becomes simply a barrier as might be used in a conventional cleanroom to restrict access.

Isolator Facility

High throughput isolator design has an open isolator (protected by air overpressure) in a surrounding room of ISO 8 (Class 100,000). The isolator provides an ISO 5 environment within which the filling process is performed. The pressure differential between the isolator and the surrounding room is continuously monitored and alarmed. Container feed is from a continuous tunnel. Isolators allow components to be fed to the supply hoppers either directly from other isolators in which bags of sterile supplies are surface decontaminated, or through a Rapid Transfer Port (RTP), and discharge to the surrounding room through an opening (often called a mouse hole) with sufficient air flow to effect an air overspill seal. Decontamination of the isolator enclosure and enclosed surfaces is accomplished using an automated system (using H₂O₂ or other sporicidal agents) that can be validated to provide a four-to-six-log reduction of a highly resistant biological indicator as stipulated in FDA's 2004 aseptic processing guidance.¹⁰ Control of the environment is focused on the isolator enclosure and contained equipment, as the surrounding ISO 8 room requires a substantially lower degree of control. Personnel may wear uniforms with hair/beard covering and gloves when using the isolator gloves. The operators use the isolator gloves to perform set-up, environmental monitoring, and any interventions. Quite often isolator-based filling equipment is sterilized and cleaned-in-place and interventions for routine tasks such as replenishment of supplies may be accomplished using automation.

Evaluation Criteria

The impact of the decision process is of such magnitude that considerable deliberation should be given to each of the relevant factors. The evaluation process should address each of the following: facility lead time; initial facility cost; qualification duration; qualification obstacles; operating cost; operational hurdles; line preparation; environmental sanitization; line operation; environmental monitoring; process simulation; impact of personnel; cleaning; change over; suitability for campaign usage; system maintenance; complexity; novelty; regulatory expectations; industry perspectives and intangibles.

Facility Lead Time - The time period required to bring the facility into full operation exclusive of the qualification/validation period.

Initial Facility Cost - The installed cost for the facility, including infrastructure, facility systems, and process equipment.

Qualification Duration - The time required to complete the qualification of the facility, including environmental control systems or isolator decontamination.

Qualification Obstacles - Unique problems associated with the technology choices that hinder the completion of the qualification/validation effort.

Operating Cost - Cost to operate the facility, including utilities, personnel, sanitization materials and labor, environmental monitoring (including cost of testing), gowning materials, and consumables.

Operational Hurdles - Difficulties associated with the use of technology for aseptic filling.

Line Preparation - Those activities required to ready the line for filling.

Environmental Sanitization - The methods used for disinfection/sanitization of the processing environment or the decontamination of the isolator.

Line Operation - Impact on the routine use of the line.

Environmental Monitoring - The requirements for periodic sampling of the processing environment.

Process Simulation - Media fill execution as required initially and periodically.

Impact of Personnel - The extent to which personnel practices can influence aseptic operations.

Cleaning - Methods for cleaning product contact and non-product contact parts.

Change Over - Conversion of the line from one size/format to another.

Suitability for Campaign Usage - Considerations relative to the repetitive use of the line for the same product format.

System Maintenance - Impact of system maintenance during the aseptic filling operation.

Complexity - The overall complexity of the facility and its equipment.

Containment Utility - The potential for utilization of the facility for the aseptic processing of potent compounds.

Regulatory Views - The perception of the technology from the perspective of the inspector/reviewer.

Industry Perspectives - The end users' views of the technology.

Intangibles - Factors not specifically addressed in the prior elements.

Overall Assessment

RABS designs have features in common with conventional, manned cleanroom technology and with isolation technology. Table A highlights some of the common features of these systems. Passive RABS are substantially closer in both concept and capability to the more evolved cleanroom designs that have utilized rigid and semi-rigid barriers between the operator and the critical aseptic fill zone. Active RABS are closer in design to open isolators, the primary differences being the mode of sanitization-decontamination and the aerodynamic separation mechanisms, i.e., air overspill for RABS and defined positive pressure differentials for isolators.

As first conceived, RABS were intended to offer the performance advantages of isolators at less cost and with fewer qualification/validation hurdles. The recent increased interest in RABS as a concept appears to have been an outgrowth of less than fully successful isolator projects, stimulated by the hope that the technology would mitigate the more difficult aspects of isolation technology design and validation, which in the past had contributed to rather long project timelines. However, in recent years, the isolator design, validation, and regulatory compliance issues have been mostly resolved. While there are benefits to some RABS concepts relative to cleanrooms, RABS can realize only some of the benefits of isolation and dramatically reduce process design and validation efforts relative to isolators. Over the last several years, isolator technology has been implemented successfully many times and the regulatory authorities will continue to favor it as the aseptic processing approach that comes closest to fully eliminating risk from human contamination. The number of isolators in use each year continues to grow, and they have performed very well.¹¹

There are several multi-national firms that have had such success with isolators that they presently operate more than 20 units worldwide. However, success has not been limited to large and well-financed projects; each of us has worked with smaller firms whose first (and only) aseptic fill operation is isolator-based. Projects that utilize a clear statement of user requirements (and those where those requirements are realistic rather than arbitrary) have consistently delivered successful outcomes.

The key issue is whether or not RABS and isolator performance can be considered equivalent. If that were the case, then the less expensive RABS design should prevail with isolators reserved only for those applications where a RABS is inadequate for the task because of operational considerations. Of course, the previous statement assumes that RABS are truly less expensive than isolators, but when full facility and operational costs are factored in, this is far from certain.¹²

Aseptic Filling

Project Concern	Conventional	RABS	Isolator
Facility Lead Time	<ul style="list-style-type: none"> Building infrastructure time consuming due to significant classified clean space requirements Permitting/site activities more complex More project elements/vendors 	<ul style="list-style-type: none"> Building infrastructure time consuming, because clean space requirements are effectively the same as conventional Facility activities more complex More project elements and vendors involved 	<ul style="list-style-type: none"> Lead time for isolator equipment is typically shorter than that for an ISO 5 controlled environment facility. Equipment more complex, but facility simpler
Initial Facility Cost	<ul style="list-style-type: none"> Costs well defined historically Costs for architecture and engineering as well as HVAC systems can be substantial Large footprint of higher classified environments 	<ul style="list-style-type: none"> Costs higher than conventional Costs for architecture and engineering as well as HVAC systems can be substantial More equipment related costs Large footprint of higher classified environments 	<ul style="list-style-type: none"> Isolator equipment is more expensive Is higher cost justified or is it added vendor margin? Costs less certain at project start
Qualification Duration	<ul style="list-style-type: none"> 6 to 9 months typical No new issues 	<ul style="list-style-type: none"> 6 to 9 months typical Could theoretically avoid some of the more controversial aspects of isolators, May result in new requirements that have their own controversies 	<ul style="list-style-type: none"> 6 to 9 months typical Longer periods are a reflection of excess requirements rather than any insurmountable technical hurdle
Qualification Obstacles	<ul style="list-style-type: none"> Issues well established and easy to resolve 	<ul style="list-style-type: none"> New issues require new solutions 	<ul style="list-style-type: none"> New issues require new solutions
Operating Cost	<ul style="list-style-type: none"> Baseline 	<ul style="list-style-type: none"> Higher than conventional Few opportunities for cost reduction that are exclusive 	<ul style="list-style-type: none"> 25-30% of cleanrooms, mostly related to HVAC operating costs Other savings in gowns, supplies, labor utilization, EM
Operational Hurdles	<ul style="list-style-type: none"> None 	<ul style="list-style-type: none"> Less complex than isolators Simpler adaptation from earlier operating modes 	<ul style="list-style-type: none"> Requires many new elements Changes to old paradigms necessary
Line Preparation	<ul style="list-style-type: none"> Hands on by operators Much less secure due to operator proximity 	<ul style="list-style-type: none"> Hands on by operators Slow due to access constraints Less secure due to operator proximity 	<ul style="list-style-type: none"> Hands on by operators Slow due to access constraints Safer because of isolator
Environmental Sanitization	<ul style="list-style-type: none"> Disinfection/sanitization performed by gowned personnel Reproducibility and validation uncertain 	<ul style="list-style-type: none"> Disinfection/sanitization performed by gowned personnel Reproducibility and validation uncertain Access for anti-microbial treatment requirements not defined and still subject to discussion 	<ul style="list-style-type: none"> Reproducible decontamination with a sporicidal agent Requirements for decontamination well defined and generally harmonized Can be validated
Line Operation	<ul style="list-style-type: none"> Superior operator access More risk of contamination 	<ul style="list-style-type: none"> Restricted access slows interventions Reduced risk of contamination relative to cleanroom, less capable than isolators Open door interventions are risky 	<ul style="list-style-type: none"> Restricted access slows interventions Risk of contamination lower than for either conventional or RABS
Environmental Monitoring	<ul style="list-style-type: none"> Methods well defined Performance generally excellent but with occasional excursions 	<ul style="list-style-type: none"> Methods well defined, but some adaptation may be required Performance could be only slightly below that of isolators, but currently there is only a small experience base 	<ul style="list-style-type: none"> Methods well defined but more adaptation may be required Performance excellent
Process Simulation	<ul style="list-style-type: none"> Performance excellent 	<ul style="list-style-type: none"> Performance excellent, but currently the experience base is very limited 	<ul style="list-style-type: none"> Performance excellent
Impact of Personnel	<ul style="list-style-type: none"> Familiar environment Worker protection minimal 	<ul style="list-style-type: none"> Environment separation substantially less effective than isolators Worker protection limited 	<ul style="list-style-type: none"> Essentially removed from critical area Closed isolator enhances worker safety with potent compounds
Cleaning	<ul style="list-style-type: none"> Largely COP for product contact, CIP possible Manual cleaning of non-product contact surfaces Difficult issue when handling potent compounds 	<ul style="list-style-type: none"> Largely COP for product contact, CIP possible Manual cleaning of non-product contact surfaces Difficult issue when handling potent compounds 	<ul style="list-style-type: none"> Largely COP for product contact, complete CIP possible Manual cleaning of non-product contact surfaces Operator access slows cleaning when closed
Change Over	<ul style="list-style-type: none"> Size, component and product change all relatively easy Greater risk of microbial contamination 	<ul style="list-style-type: none"> Size, component change easy Product change requires internal cleaning Greater risk of microbial contamination 	<ul style="list-style-type: none"> Size, component change relatively easy Product change requires internal cleaning
Suitability for Campaign Usage	<ul style="list-style-type: none"> Considered easier to validate 	<ul style="list-style-type: none"> Campaign potential unknown Can potential product carryover be ignored? 	<ul style="list-style-type: none"> Conceptually easy Considered difficult to validate by some Product carryover a concern
System Maintenance	<ul style="list-style-type: none"> Dark side maintenance not widely available 	<ul style="list-style-type: none"> Dark side maintenance possible 	<ul style="list-style-type: none"> Dark side maintenance during run easy
Complexity	<ul style="list-style-type: none"> Systems are least complex 	<ul style="list-style-type: none"> Systems are less complex than isolators 	<ul style="list-style-type: none"> More controls, equipment and instrumentation required. Decontamination adds extra elements
Containment Utility	<ul style="list-style-type: none"> Limited given greatest potential for worker exposure 	<ul style="list-style-type: none"> Improved due to greater worker separation, but not absolute 	<ul style="list-style-type: none"> Near perfect for closed isolators due to presence of complete physical separation of the environments
Novelty	<ul style="list-style-type: none"> None 	<ul style="list-style-type: none"> New technology with its own limitations 	<ul style="list-style-type: none"> Some firms have almost no isolators Some firms already have substantial experience
Regulatory Views	<ul style="list-style-type: none"> Proven technology Recognized as less capable and becoming obsolete 	<ul style="list-style-type: none"> Well accepted proven technology Recognized as less capable than isolators 	<ul style="list-style-type: none"> Considered superior, but cautions still raised More rapid implementation outside US.
Industry Perspectives	<ul style="list-style-type: none"> Proven technology with known limitations 	<ul style="list-style-type: none"> Largely proven technology with known limitations Few uncertainties 	<ul style="list-style-type: none"> Embraced by some, avoided by others Unproven technology, can lead to uncontrollable project costs
Intangibles	<ul style="list-style-type: none"> Easy to implement Not the latest nor the safest approach Mature design may limit useful lifetime. Will it be GMP in 10 years time? 	<ul style="list-style-type: none"> Easy to implement Not the latest nor the safest approach Further advances may not be possible 	<ul style="list-style-type: none"> More capable once fully operational Now fairly well established technology. Further advances in design are underway

Note 1: The entries presented in the table reflect the opinions of the authors, drawing upon our 40 years of experience as consultants, and nearly 100 years working with sterile products technology.
 Note 2: Shaded boxes indicate where essentially the same situation prevails with more than one technology.

Table A. Aseptic Filling Technology Comparison.

The primary technical differences between RABS and isolator designs lie in the following areas:

- Isolator decontamination is performed by an automated system and can be validated to provide multiple-log spore reduction. RABS are manually disinfected by gowned personnel.
- RABS do not provide a complete physical separation between the internal and external environments. Isolators maintain a continuous pressure differential with respect to the environment or are closed.
- Passive RABS must be positioned in an ISO 5 environment, while isolators have been successfully operated in an ISO 8 environment.¹³
- RABS are poorly suited for containment applications, an increasingly important concern as drugs become increasingly potent. Closed isolators provide the highest degree of separation currently available, providing worker protection while shielding the aseptic zone from worker-borne contamination.

It seems to us that these differences are meaningful enough to make the choice relatively easy. The ability to reliably decontaminate isolators using an automated system is a major advantage. This eliminates the vagaries and uncertainties of manual disinfection that are time-consuming, less than fully effective, and hazardous to personnel. The efforts required to initially validate isolator decontamination may be greater (we have not experienced any substantial difficulty in our recent efforts, but we have heard this regarding projects with which we have not been involved), nevertheless the increased reliability and robustness of isolation decontamination is difficult to ignore. The majority of isolators have been installed in ISO 8 (Class 100,000) environments where the operating requirements are relatively easy. Passive RABS designs, even those without “open door” interventions, should be in ISO 5 environments since there is no pressure differential between the interior and exterior of the enclosure. An ISO 5 background for the RABS mandates periodic sanitization, aseptic gowning, and environmental monitoring in the background environment at a level commensurate with manned cleanrooms. ISO 7 environments may be suitable for active RABS designs operated without “open door” interventions. For containment applications, the superiority of closed isolators to all other technologies is unquestioned.

RABS is an interesting offshoot in the continued evolution of aseptic processing technology. Unfortunately, it can sometimes be a “Back to the Future, Forward to the Past” approach. It seems inappropriate to remove what are some of the more beneficial design features in isolators and revert to what is essentially a sophisticated barrier system of the type that has been used for many years. Isolators represent the future of aseptic processing in our industry; we owe ourselves

and the patients who take the drugs we produce the best available technology we can provide.

References

1. *ISPE Baseline® Pharmaceutical Engineering Guide, Volume 3 - Sterile Manufacturing Facilities*, International Society for Pharmaceutical Engineering (ISPE), First Edition, January 1999, www.ispe.org.
2. ISPE RABS Definition.
3. Agalloco, J. P., J. E. Akers, et al. (2001), “Technical Report No. 34, Design and Validation of Isolator Systems for the Manufacturing and Testing of Health Care Products,” *PDA J. Pharmaceutical Science and Technology*, 55 (5, Supplement).
4. www.medinstill.com.
5. Verjans, B., J. Thilly, et al. (2005). “A New Concept in Aseptic Filling: Closed-Vial Technology,” *Pharmaceutical Technology Aseptic Processing Supplement*: s24-s29.
6. ISO 14644-1.
7. Anonymous (1992). FED-STD-209E. Airborne Particulate Cleanliness Classes in Cleanrooms and Clean Zones, U. S. General Services Administration.
8. Annex 1.
9. ISPE, Restricted Access Barrier Systems (RABS) for Aseptic Processing Definition, 16 August 2005.
10. FDA (2004), Guidance for Industry, Sterile Products Produced by Aseptic Processing - Current Good Manufacturing Practice.
11. Lysford, J. and Porter, M. “Barrier Isolation History and Trends,” ISPE Washington Conference: Barrier Isolation Technology, 2 June 2004.
12. Agalloco, J., Akers, J., and Madsen, R. Private communications with clients.
13. Some proponents of RABS have suggested that the units can be opened to the surrounding environment in the midst of the aseptic process to perform an intervention, followed by disinfection and a resumption of the process. This seems to be a risky practice that should be avoided. We have not considered this practice, and restricted our discussion to RABS that are operated without “open door” interventions of any kind. If “open door” interventions are contemplated in the operation of the RABS, then conformance to the EU Annex 1 background requirements of ISO 5 should be maintained at all times (including when the RABS is closed).

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This article compares the use of Restricted Access Barrier Systems (RABS) and Isolator Systems for product final fill operations.

Advanced Aseptic Processing: RABS and Isolator Operations

by Eric A. Isberg

Advanced Aseptic Processing (AAP) is a term referenced in the recently published ISPE RABS definition¹ to cover the spectrum of Restricted Access Barrier Systems (RABS) and isolator systems. In general, AAP techniques are physical barrier methods of product protection and containment that are used during manufacturing operations to separate (primarily) operators from the process. These methods are most often used during open processes or other critical process steps to ensure product is not exposed to viable organisms and particulate contamination. While there are many methods to choose from, there is no argument that AAP techniques are widely used.

Complete and absolute ingress control is essential to AAP operation, and is essential to ensure an improvement over traditional open cleanroom processing. Operations within equipment like Laminar Flow Hoods (LFHs) or Biosafety Cabinets (BSCs) do not fit within the definition of AAP, as this equipment only provides partial separation (i.e., the hands and arms of the operators are not physically separated from the process when using this equipment). Curtained cleanroom areas also are not in this definition, as curtains provide little real barrier from ingress. Only complete, rigid wall enclosures fall within the scope of AAP.

The focus of this article is to compare the use of RABS and isolators for product final fill operations. It will give a very general overview of both systems. It will then describe key mechanical and operational areas in which the two systems differ, while at the same time highlighting several key operational areas where they do not. Finally, it will propose that either system, if operated correctly according to approved procedures, will work successfully to ensure an improvement over traditional open cleanroom processing.

RABS and Isolator Overview

The ISPE RABS definition¹ describes the common characteristics of a RABS system. The system has an ISO Class 5 environment² with unidirectional airflow enclosed in a rigid wall enclosure with glove port access where necessary. The interior of the enclosure is manually sanitized with sterilized equipment and parts introduced using aseptic procedures which can include transfer systems. Because the system is open to the surrounding room, it is commonly located in an ISO Class 7 or better environment.² All product or process contact parts within a RABS are sterilized or Steamed-In-Place (SIP) prior to use. Although doors can be opened, this only happens rarely, after which appropriate line clearance and cleaning must occur per procedures.

Closed RABS, like isolators, fully enclose and seal the work area, and supply the interior with HEPA filtered air that is returned through sealed ductwork. The main difference between closed RABS and isolators is that closed RABS have no automated bio-decontamination cycle using H₂O₂ vapor or another sanitant. The interior of the closed RABS unit is bio-decontaminated manually using cleaning solutions. One purpose for closed RABS units is for highly potent compounds, where personnel protection is the purpose for product containment. In this case, they are designed as containment RABS, which require special leak tightness requirements, air filtration systems, and decontamination processes for safe operation.

Isolators are fully enclosed and sealed units with HEPA filtered air supplied in a unidirectional manner to the ISO Class 5 interior.² Completely closed isolators may be supplied with either turbulent air or unidirectional air. Air is typically recirculated by returning it to the air handlers through sealed ductwork. The chamber is bio-decontaminated via an auto-

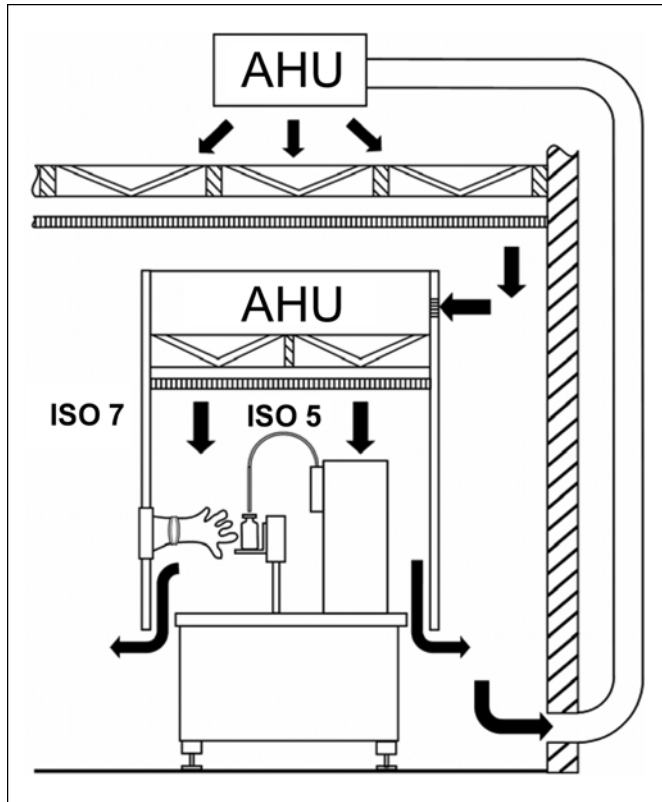


Figure 1. Basic RABS airflow diagram.

ated cycle using H_2O_2 or another sanitant. All access is through glove ports and sterile transfer systems. All items entering the system after bio-decontamination are pre-sterilized. Because they are sealed, isolators are commonly located in ISO Class 8 environments.²

Air Handling Differences

RABS systems operate in a similar fashion as LFHs in that they are fed clean air from fan units through HEPA filters and the air vents from the unit into the surrounding room - *Figure 1*. The air is unidirectional via diffuser panels and multiple fan/HEPA filter locations. Therefore, the air handling requirements are relatively uncomplicated. Pressure balancing involving supply and return ductwork and return fans are not required. The exception to this is closed RABS, which can have a pressure differential to the outside room and therefore behave like an isolator in regard to basic air handling requirements.

Basic isolator air handling requirements are more complicated than RABS - *Figure 2*. Air is re-circulated so return fans and ductwork are required. In order to maintain positive pressure, a large part of the air handling unit, including the return ductwork, must be leak tight. Leak testing of the system, which involves recording pressure decay over time, is required to prove the unit is sealed prior to sanitization and operation. Ductwork that leads outside of the cleanroom, and outside of the building, is often required to safely vent H_2O_2 vapor after sanitization where this chemical is used.

The bio-decontamination cycles for isolator units are mechanically complicated. For example, before injection of the

H_2O_2 vapor (when used), the chamber and air handling ductwork must be conditioned. The purpose of the conditioning is to ensure a sufficient concentration of H_2O_2 vapor is injected into the system and that the H_2O_2 stays in vapor form during the cycle. Conditioning consists of heating the chamber and ductwork and lowering the humidity of the air in the system for low humidity bio-decontamination systems. High humidity bio-decontamination systems do not require humidity control during conditioning. After the bio-decontamination cycle is complete, out gassing of the H_2O_2 vapor is required to bring the concentration down to levels that are both safe for personnel, yet not high enough to affect the product being filled. Heating, Ventilation, and Air Conditioning (HVAC) systems are often required to perform these functions.

For smaller systems, the conditioning, bio-decontamination, and aeration events can be performed using self-contained, external bio-decontamination systems. However, for larger isolator systems, multiple external bio-decontamination systems are often necessary, along with the HVAC system. These systems must be tied together to 'act as one' during bio-decontamination. One alternative is to have an integrated HVAC and bio-decontamination system. The advantage of this is that air handling, bio-decontamination, aeration, and overall pressure balance can be controlled by the same unit.

Cleaning and Bio-Decontamination Differences

The interior of isolators are bio-decontaminated using an automatic sequence which most often includes injection of H_2O_2 vapor as the sanitant. These cycles are very consistent and lead to a validatable bio-decontamination method. However, manual cleaning of the interior is still required on a

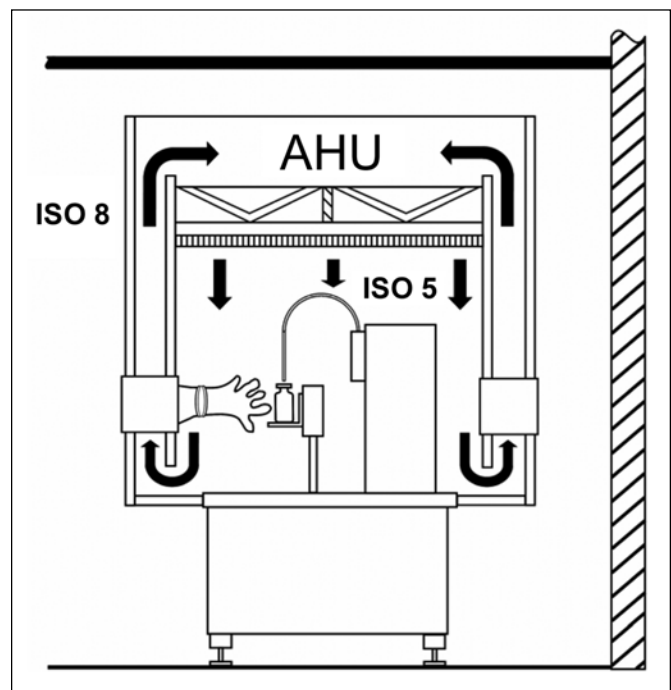


Figure 2. Basic Isolator airflow diagram.

regular basis. Direct contact cleaning is required to remove surface contaminants and to reduce the likelihood of biofilm formation. Also, manual cleaning is often required whenever the chamber is opened for parts changeover and other invasive events. Procedures should dictate when isolators are manually cleaned.

As described in the ISPE RABS definition,¹ the bio-decontamination of RABS units is not automatic. Manual spray and wipedown methods must be employed. The difficulty lies in performing consistent, repeatable, and complete bio-decontamination using manual methods. Validation of the effectiveness of the cleaning and bio-decontamination solutions is an important step in justifying manual cleaning processes. In many cases, companies are trying to move away from manual cleaning and bio-decontamination because of consistency issues and the difficulty of validating manual methods. Alternatively, some companies offer periodic cleanroom bio-decontamination services using automated equipment that can be used for RABS systems.

Environmental Monitoring

Environmental monitoring for both viable and non-viable particulates is key to determining classification levels in cleanroom space. Ongoing monitoring is required to show that the system maintains an ISO Class 5 environment over time.²

Isolator particulate and microbiological monitoring can only be achieved via built-in sampling ports or by transferring pre-sterilized sampling devices and sampling plates into the isolator in a sterile manner. Planning for environmental monitoring, including sampling methods, location of sampling devices, and frequency of sampling, must be part of the isolator system design considerations.

Environmental monitoring via built-in sampling ports or by transferring pre-sterilized sampling devices and sampling plates also can be used for RABS. However, RABS units often have openings near floor level for air to flow out of the interior of the chamber. Therefore, there is the option of using portable sampling devices that have sampling probes that are inserted into these openings.

Personnel Gowning

Operators must gown according to the classification of the area surrounding the AAP system. In the case of isolators, the gowning is often for an ISO 8 area.² ISO 8 gowning is often comprised of items like a plant uniform or jumpsuit, lab coat, head cover, and shoe covers. Single gloves are often used as a precaution during work using the isolator glove ports.

For RABS, the gowning must be for the ISO 7 or better environment² where the equipment is located. This can include the addition of full, sterile one-piece suits, sterile face masks, sterile head and shoe covers, goggles, and multiple layers of gloves. The personnel must still use glove ports when performing work within the RABS. Obviously, personnel comfort is a factor in RABS operation.

Glove Replacement and Testing

One area in which RABS and isolators do not differ is in the way that glove-port gloves and gauntlets are controlled. They must be sterilized prior to use, either by bio-decontamination or sterilization processes. The gloves also require inspection prior to use, and periodic replacement is necessary to ensure effectiveness. A system of glove integrity testing and/or mechanical inspection may be required to provide evidence that leaks do not exist, as leaks can compromise the ISO Class 5 environments within the barrier system.

Built-in, automated glove testing systems are available with some RABS and isolator systems. These automated systems have the advantage of speed, as glove ports can be tested simultaneously, and of accuracy compared to manual methods.

Procedural Requirements

A “paradigm shift” is required by an organization to go from traditional open cleanroom processing to RABS and/or isolator use. All unit operations, including manufacturing, maintenance, quality, validation, and other functions, must prepare for this shift. Because processes will change and new processes will be required, Standard Operating Procedures (SOPs) must be created to govern them.

Adherence to new and revised SOPs is essential to ensure RABS and isolators are operated successfully. SOP requirements are more critical to RABS operation because there are more manual operations, such as the new bio-decontamination processes that will be required. However, if SOPs are written well and are followed by all personnel, either AAP method can be performed successfully.

Conclusions

Restricted Access Barrier Systems (RABS) and isolator systems are two methods of Advanced Aseptic Processing (AAP) that ensure an improved processing environment for cleanroom operations. Knowing some of the key mechanical and operational areas in which the two systems differ will increase awareness of the systems in the industry, and will help create a more detailed definition of each.

These two AAP methods may, on first glance, appear to be very similar. Both methods provide ISO Class 5 cleanroom space and fully separate the operators from the process. However, of the two systems, only isolators are widely accepted within the industry for use in product fill operations. This is because RABS has been used in the past to label a wide variety of containment systems. Hopefully, the new ISPE RABS definition, along with detailed AAP system comparisons like this one, will help by increasing knowledge of how each system can be used successfully to ensure an improvement over traditional open cleanroom processing.

References

1. Restricted Access Barrier Systems (RABS) for Aseptic Processing, ISPE Definition, 16 August 2005.


2. International Standard ISO 14644-1:1999(E) Cleanrooms and Associated Environments – Part 1: Classification of air cleanliness.

About the Author



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This article reviews the physical chemistry of the safe production of hydrogen peroxide vapor and how to maintain a constant concentration of the vapor in a chamber. This article also reviews the calculations and procedures used to obtain the maximum concentration of vapor without allowing condensation of liquid to occur.

The Physical Chemistry of Decontamination with Gaseous Hydrogen Peroxide

by Carl Hultman, Aaron Hill, and Gerald McDonnell

Introduction

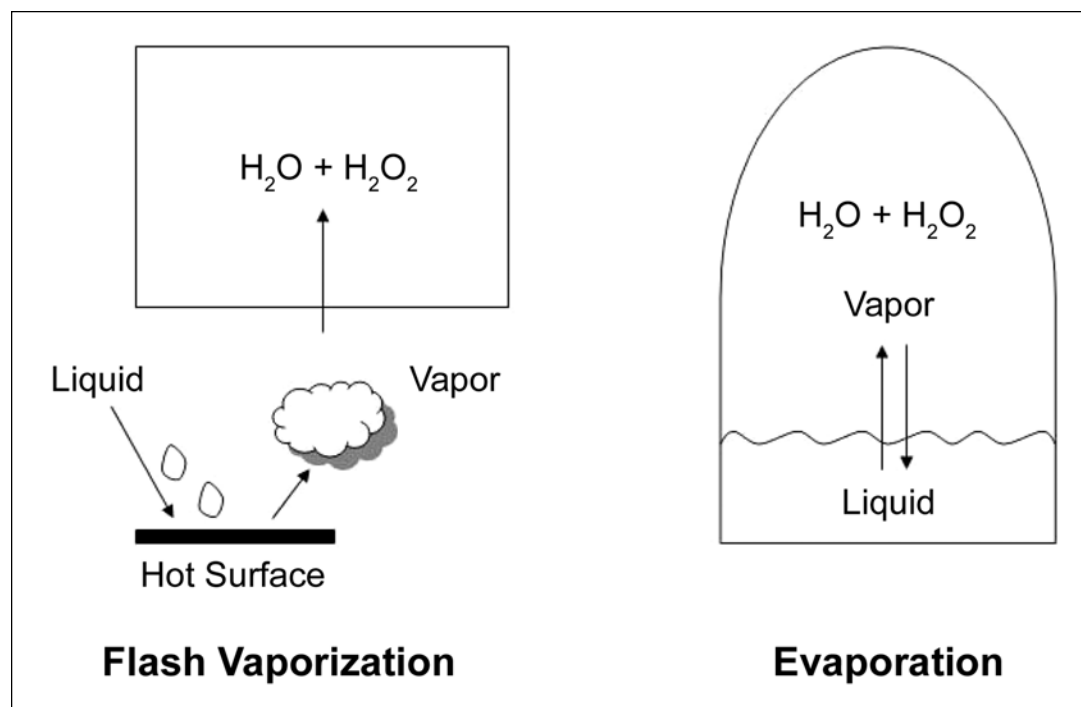
The decontamination of surfaces contaminated with microorganisms within critical, enclosed areas is an important consideration to pharmaceutical, research, and other facilities. A safe and reliable way to decontaminate hard surfaces (including those in isolators, laminar flow cabinets, and cleanrooms) involves exposing the surfaces to gas-phase hydrogen peroxide.^{1,2,3} Gas phase hydrogen peroxide is a known rapid, broad-spectrum antimicrobial which, as part of a controlled process, can allow for reproducible area decontamination. Hydrogen peroxide also has a rather safe profile, both from a user and environmental perspective, in comparison to traditional fumigation methods that have used

formaldehyde, ethylene oxide, or propylene oxide gas. An understanding of the physical chemistry behind the generation and control of gaseous hydrogen peroxide is important to optimize the safety, efficacy, and reproducibility of a given decontamination process. This article discusses the physical chemistry behind a typical process and the procedures needed to achieve optimal decontamination using gaseous hydrogen peroxide.

Liquid and Gaseous Hydrogen Peroxide

Hydrogen peroxide (H_2O_2) is widely used as an antiseptic, disinfectant, and sterilant.⁴ It is a desirable biocide because it demonstrates broad spectrum antimicrobial activity, has low toxic-

Figure 1. Hydrogen peroxide vaporization processes.



Hydrogen Peroxide Weight	(%w/v)	t = 25 C
Vapor	Liquid	
1.87	32.1	
8.0	55.7	
24.1	73.9	
35	77.8	
56.4	88.3	

Table A. Equilibrium concentrations of hydrogen peroxide vapor that will form (evaporate) over liquid hydrogen peroxide (see Figure 1, *Evaporation*).

ity, and breaks down into water and oxygen in the environment. For example, liquid hydrogen peroxide solution is used directly on the skin at up to 6% w/v and at higher concentrations as a general surface disinfectant. Pure hydrogen peroxide exists as a liquid at room temperature (25°C) and atmospheric pressure (101.35kPa). For antimicrobial applications, greater efficacy is observed as the concentration is increased, which is particularly important to achieve sporicidal activity; however, at high concentrations, liquid hydrogen peroxide is unstable/reactive and may be explosive or undergo spontaneous combustion depending on how it is handled.^{5,6} Therefore, liquid preparations are used at lower concentrations diluted in water (generally 3 to 59% by weight) and often in synergistic formulations with other biocides (including peracetic acid). The antimicrobial activity of hydrogen peroxide is dramatically increased when in a gaseous phase. For example, the efficacy of hydrogen peroxide against bacterial spores has been shown to be similar at a gaseous concentration of 1mg/L in comparison to ~400mg/L in liquid.⁵ To generate the gas, it is necessary to heat liquid hydrogen peroxide, generally by flash vaporization on a hot surface that will be discussed in more detail. Under these gaseous conditions, even lower concentrations (~0.1mg/L) of peroxide are rapidly antimicrobial and may be used to achieve sporicidal activity.

A further consideration in the comparison of liquid and gaseous peroxide is material compatibility; attention should be focused on two factors when considering surface contact:

1. the effect of the material on the decomposition rate of the peroxide (therefore loss of activity)
2. the effect of hydrogen peroxide on the material itself.

With liquid hydrogen peroxide (of about 45% by weight or more), the possibility of forming detonatable mixtures on reaction with organic substances may exist. Commonly used materials have been categorized into four different classes according to the suitability of exposing these materials to liquid concentrations equal to or higher than 90% by weight of peroxide in water.⁷ Of note, Class 4 materials may cause decomposition of hydrogen peroxide, and particularly with concentrated liquid peroxide, cause damage to the surface or form explosive mixtures. Some of these Class 4 materials include wood products and polymers such as neoprene, buna rubber, silicone rubber, and tygon. These materials may undergo degradation and/or cause spontaneous combustion. Other Class 4 metals, including copper, lead, magnesium

alloys, and stellite #6, act as catalysts that accelerate the decomposition of peroxide and also may encourage combustion when in contact with other materials. Lubricants such as silicones, paraffin, and aroclors also are Class 4 materials. Highly concentrated solutions of peroxide also may degrade certain electrical components or other materials; an example is that liquid hydrogen peroxide can attack the plasticizers in PolyVinyl Chloride (PVC), thus making the surface brittle after extended exposure. Additionally, certain grades of stainless steel, such as 304 grade, can show slight corrosion or discoloration for liquid peroxide solutions ranging from 10 to 100% by weight.

Hydrogen Peroxide Evaporation and Condensation

Hydrogen peroxide vapor can be conveniently produced from hydrogen peroxide/water solutions by two distinct processes, evaporation and flash vaporization - *Figure 1*. It is important to note that both processes will produce different concentrations of hydrogen peroxide vapor in a given volume. When liquid hydrogen peroxide is allowed to evaporate into a dry, enclosed space, the concentration of hydrogen peroxide in the vapor state is much lower than the concentration in liquid state - *Figure 2*. This occurs because the water leaves the mixture at a higher rate than the peroxide due to the higher vapor pressure of water. For instance, if a 35% (by mass) hydrogen peroxide/65% water mixture evaporates into a dry enclosed space at 25°C, the resulting gas will consist of 2.15% (by mass) hydrogen peroxide and 97.85% water at saturation. Saturation refers to the point at which the air can not hold further peroxide/water and at which point condensation (or precipitation) or water/peroxide will occur. The concentration at which this occurs (referred to as the 'dew' point) can be predicted based on the peroxide/water concentrations, and the temperature of the gas - *Figure 2*. A detailed discussion of this phenomenon is discussed in the literature.⁵

The evaporation rate can be increased by applying an energy source, for example heat can be applied to boil the peroxide/water solution. Since water has a lower boiling point than hydrogen peroxide, the water will vaporize at a higher rate, giving a higher concentration of water in the gaseous state and an increased concentration of hydrogen peroxide in liquid state. With time, the higher peroxide liquid concentration may become unsuitable for materials in contact with the liquid and can pose a safety risk.

The equilibrium concentration of peroxide in the vapor over a liquid is always lower than the concentration in the liquid. Table 1 shows the concentration of peroxide in the vapor over liquid solutions at different peroxide concentrations at 25°C. The equilibrium concentration of peroxide in the vapor is always lower because the water escapes the liquid at a higher rate than the peroxide. The reverse is true when peroxide/water vapor condenses to the liquid state. As shown in Table A, the equilibrium concentration of the liquid formed when a vapor of 35% by weight peroxide condenses is about 77.8% by weight peroxide. This is because the peroxide in the vapor has a greater desire to enter the liquid state than

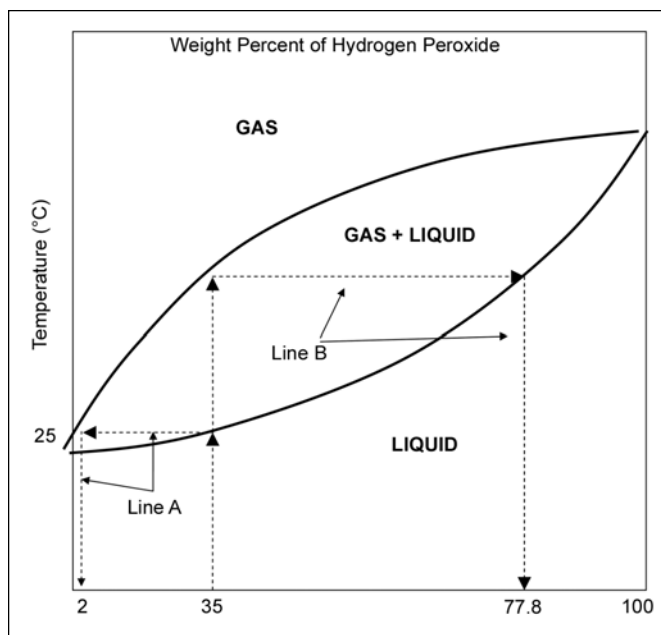


Figure 2. A representation of the Hydrogen Peroxide/Water Phase Diagram. The upper solid line indicates the point at which the gas mixture is formed (note higher concentrations at higher temperatures) and the lower solid line when liquid is present. Line A shows the conversion of 35% liquid peroxide/water mixture (at 25°C) to vapor at ~2% peroxide. Line B shows the condensation of 35% gaseous peroxide/water mixture to liquid at ~78%.

the water in the vapor. Therefore, the peroxide condenses at a higher rate than the water, causing the higher concentration of peroxide in the resulting liquid.

Flash vaporization is a distinct process which can be achieved by applying energy, e.g., by direct application of a peroxide/water mixture to a hot surface - *Figure 1*. Flash vaporization forces the water and hydrogen peroxide in the liquid solution to evaporate *simultaneously*, thereby producing gaseous concentrations of water and peroxide at approximately the same concentration as the starting liquid mixture. The gas concentration will stay constant as long as condensation does not occur. Table B shows the concentrations of hydrogen peroxide that will saturate the vapor and cause condensation. If the gas concentration is increased above saturation or if cooled to below the dew point, condensation will occur. For example, when condensation occurs with a gas at ~35% by weight peroxide it will condense as a liquid at ~77.8% by weight peroxide - *Figure 2*.

Physical Chemistry

The vapor pressures of gases over multi-component liquid solutions may be calculated using the following equations:^{5,8,9}

$$P_{p(gas)} = X_{p(liq)} Y_p P_p^o \quad (1)$$

$$P_{w(gas)} = X_{w(liq)} Y_w P_w^o \quad (2)$$

$$Y_{w(liquid)} = \exp\left[\frac{(1-X_w)^2}{RT}\right] (B_0 + B_1(1 - 4X_w) + B_2(1 - 2X_w)(1 - 6X_w)) \quad (3)$$

$$Y_{p(liquid)} = \exp\left[\frac{X_w^2}{RT}\right] (B_0 + B_1(3 - 4X_w) + B_2(1 - 2X_w)(5 - 6X_w)) \quad (4)$$

where:

- $P_{p(gas)}$ is the vapor pressure of the peroxide in the vapor in atmospheres
- $P_{w(gas)}$ is the vapor pressure of water in the vapor in atmospheres
- X_p and X_w are the mole fractions of peroxide and water respectively in the liquid
- Y_p and Y_w are the activity coefficients for peroxide and water respectively in liquid solution

P_p^o and P_w^o are the equilibrium vapor pressures in atmospheres of pure peroxide and water respectively at the temperature of interest. B_0 , B_1 , and B_2 are empirically determined constants for hydrogen peroxide with the values shown below.

$$B_0 = -752 + 0.97t \quad t \text{ in degrees centigrade}$$

$$B_1 = 85$$

$$B_2 = 13$$

Vapor pressure data may be converted into gas phase concentration units of mg gas per liter using the ideal gas equation as shown below.

$$\text{mg/liter} = P(\text{Mol Wt})(1000 \text{ mg/g})/RT \quad (5)$$

The concentration in mg/liter calculated from equation five is the concentration at a given temperature that will cause condensation, where, P is pressure in atmospheres, Mol Wt is the molecular weight of the gas of interest in grams/mole, R is the ideal gas constant 0.082 latm/deg mole, and T is temperature (°K).

Achieving Optimal Concentration of Peroxide in Vapor Form

As more vapor at a composition of 35% by weight peroxide is introduced into an enclosed chamber, the pressure and concentrations of the peroxide/water vapor in the chamber will increase. Eventually, a high enough concentration (expressed in mg/liter) will be reached at the operating temperature to cause the undesirable condensation of liquid in the chamber. The maximum allowable concentration of peroxide in the vapor that will not cause condensation may be calculated using Equations one through five. One of the complications associated with condensation is that undesirable high concentrations of peroxide liquid solutions will be formed on surfaces. Also, as liquid condenses, it may not uniformly cover all solid surfaces which may lead to non-uniform disinfection/sterilization of surfaces. Other complications associated with condensation will be elaborated on in a later section. The gaseous state for hydrogen peroxide when used for decontamination is advantageous because:

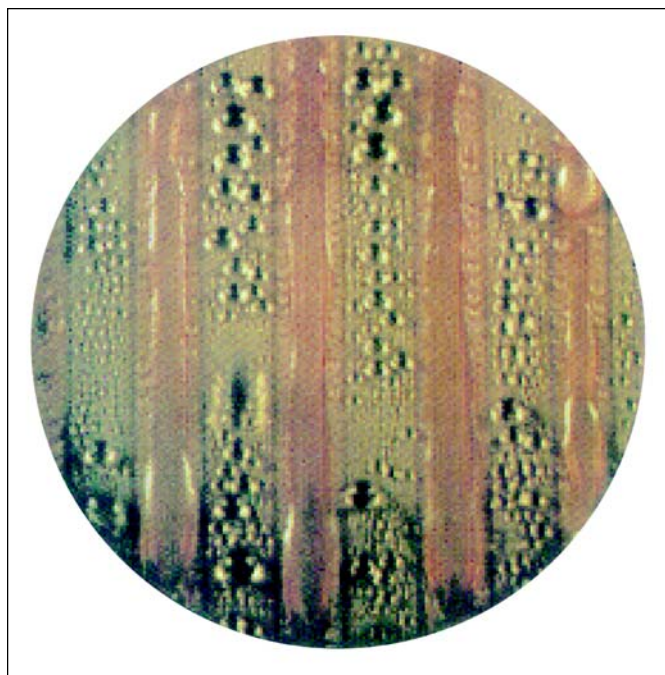


Figure 3. Dropwise condensation on contaminated metal surface.

1. Gas will have uniform contact with all exposed surfaces, thus assuring that all surfaces are uniformly decontaminated.
2. Gas will have uniform contact with surfaces with complex topographies. Examples include horizontal or vertical surfaces, cracks, and complex curvatures.
3. Gas may be safely maintained in the chamber.
4. Gas may be efficiently and quickly removed from the chamber at the end of a given decontamination time thus decreasing cycle time.

As the antimicrobial efficacy increases with increased peroxide concentration, it is desirable to get the peroxide concentration in the gas as high as possible in the chamber without having condensation occur. It is possible to calculate the maximum pressure (and/or concentration) of peroxide (or mg/L of peroxide in the chamber) that will initiate condensation using Equations one through five by knowing:

1. the concentration of the flash vaporized gas being used to fill the chamber
2. the total pressure in the chamber
3. the humidity in the carrier gas (e.g., air used to circulate gas into and out of the chamber showing the design of the decontamination system - Figure 4) and the decontamination chamber
4. the chamber temperature^{5,8,9}

As these equations can often be time consuming to do by hand, computer programs have been developed to calculate the optimum decontamination conditions for any given enclosed volume.¹⁰ Table B shows examples of the maximum peroxide concentration allowed in the chamber to prevent condensation of liquid at various temperatures at two different humidity levels for the carrier gas. Calculations assumed flash vaporization of 35% by weight peroxide. Note that increasing the relative humidity in the carrier gas decreases the maximum concentration of peroxide that may be achieved in the decontamination chamber.

Why Condensation Should be Avoided

As described above, high concentration of peroxide in the liquid state (as occurs with condensation) can be antimicrobial, but also poses some further disadvantages. The first is material compatibility. As shown in Figure 1 and Table A, the concentration of a liquid formed when 35% by weight gas condenses will be about 78% by weight peroxide. This is higher than the recommended maximum concentration of 45% by weight peroxide to assure suitable interactions with other materials. As discussed above, this peroxide concentration or higher may not only cause spontaneous combustion and also may accelerate decomposition of peroxide or cause degradation of materials. Incompatible materials can include painted surfaces and electronics. Peroxide condensation also can decrease the useful life of chamber materials in particular, those used in flexible-walled isolators. Once the condensate is formed it will eventually have to be evaporated from the chamber as peroxide is removed at the end of a decontamination phase. The slow evaporation will cause the peroxide concentration in the liquid to reach even higher unsuitable concentrations regarding safety and degradation of materials.

Decontamination reproducibility is a further concern. When condensation occurs, the surfaces in the chamber may not get uniformly exposed, depending on how condensation occurs. Condensation can occur either in a drop wise or film form, depending on the nature of the contact surface. The determining property is the surface tension of the solid surface. In general, film condensation occurs if the surface tension of the solid is at least 10 dynes/cm higher than the surface tension of the liquid condensing. The surface tension of liquid peroxide/water solutions range from 73 dynes/cm (pure water) to

Temperature(°C)	Maximum Hydrogen Peroxide Concentration (no condensation) (mg/L)	
	0% Relative Humidity Carrier Gas	10% Relative Humidity Carrier Gas
0	0.35	0.28
10	0.77	0.63
20	1.56	1.28
30	3.01	2.50
40	5.49	4.60
50	9.60	8.11
60	16.13	13.68

Table B. Maximum peroxide vapor concentration at various temperatures.

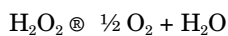
about 80 dynes/cm (pure peroxide). The surface tension for 78% by weight peroxide liquid is about 78 dynes/cm. Therefore, drop-wise condensation will occur on solid surfaces with surface tensions less than about 88 dynes/cm when gas at 35% by weight peroxide vapor is condensing. Recall that 35% by weight peroxide vapor condenses as 78% peroxide in the liquid. Polymer materials surface tensions typically range from 20 to 45 dynes/cm or lower. Therefore, drop wise condensation should occur on most polymer materials. Clean metal and glass surfaces typically have surface tensions that are higher than 200 dynes/cm. Contamination on a metal or glass surface may dramatically drop the surface tension allowing for drop wise condensation. Figure 3 shows how a contaminant on a metal surface causes drop wise condensation. This will not allow the entire surface to be exposed to liquid resulting in a non-uniform surface exposure to peroxide. Even if film wise condensation occurs, there is a possibility of non-uniform liquid exposure on the surface due to developing liquid flow patterns on vertically sloped surfaces.

A further complication associated with condensation of liquid is the additional time required to remove peroxide from the chamber at the end of an exposure phase. Gas can quickly be removed from the chamber by purging with an inert gas (such as air). Additional time is necessary to remove peroxide in the liquid form due to the time required to evaporate the liquid from all surfaces. If a material is permeable to liquid water or peroxide, additional time will be needed to remove any liquid that absorbed into the solid surface. Examples include porous materials and certain polymers, which are permeable to liquid water and/or peroxide.

Finally, condensed peroxide at high concentration may have un-suitable (even violent) reactions with certain materials in the decontamination chamber. Special safety precautions should be in place to handle any standing liquid hydrogen peroxide condensate that can be violently reactive and will cause severe burns.

Decomposition of Hydrogen Peroxide

Hydrogen peroxide, especially in gaseous form or impure liquid solutions, is not a very stable compound. In particular, it spontaneously decomposes to form oxygen and water as shown below:



Therefore, the concentration of peroxide gas in the sterilization chamber will steadily decrease over time, depending on the chamber area, material of construction, contents, etc. A simple procedure to maintain a constant peroxide concentration involves continually circulating the gas in the sterilization chamber through a system that regenerates fresh peroxide vapor as shown in Figure 4. This design is successfully used in gaseous hydrogen peroxide decontamination systems. Fresh peroxide gas produced from a flash vaporizer is introduced into the chamber as gas in the chamber is removed, thereby maintaining a consistent peroxide vapor concentration. Further, the removed peroxide gas can be

decomposed to water and oxygen in a destroyer and the water removed in a dryer. Drying the carrier gas stream is important as the water content in the carrier gas will affect the point at which condensation will occur as shown in Table B. For example, at 25°C, the maximum allowed concentration of peroxide vapor drops from 2.184 mg/liter to 1.805 mg/liter as the moisture content in the carrier gas goes from 0% RH up to 10% RH. This is a 17.4% drop in the maximum allowed peroxide concentration that may be introduced into the decontamination chamber.

Measuring and Controlling Peroxide Gas Concentration

As shown above, Equations one through five may be used to calculate the maximum level of hydrogen peroxide that may be achieved in a chamber without causing condensation. Once the maximum peroxide vapor concentration is known, it is possible to develop an operating cycle that gives the maximum concentration of peroxide while preventing condensation. The controlled variables for the cycle will include air flow rate, rate of injecting liquid peroxide into the flash vaporizer, concentration of the liquid to be flash vaporized, and the chamber temperature, volume, and humidity level. The peroxide and water concentrations during a cycle can be monitored using either infrared spectroscopy or electrochemical methods.^{10,11} It is desirable to run the peroxide concentration as high as possible, but at the same time reducing the risk of producing condensation (typically targeting less than 90% of the saturation level). It should be noted that these detector systems can only be used to monitor *gas* concentrations, where condensation of liquid will cause the sensor to fail. Overall, higher levels of peroxide vapor concentration will result in higher kill rates and therefore shorter cycle times, but it is recommended that this should be balanced by ensuring that condensation does not occur. Once the cycle is developed for a given volume and temperature, it may not be

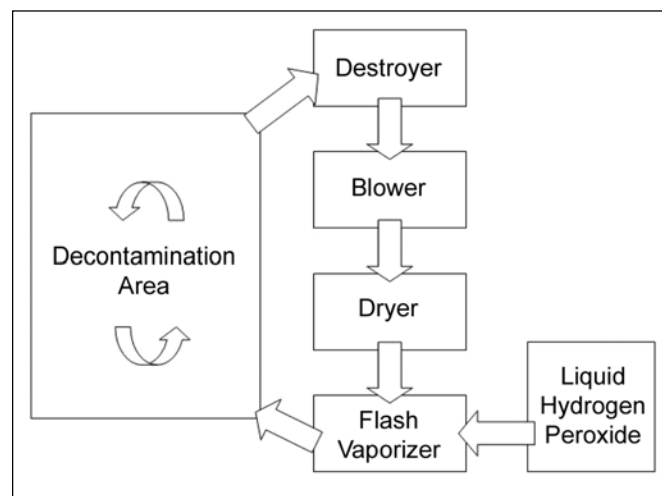


Figure 4. Typical Vaporized Hydrogen Peroxide (VHP) decontamination system. Vapor is produced by flash vaporization of liquid hydrogen peroxide and blown into a volume to be decontaminated. The vapor concentration is held constant by a constant flow of gas through a destroyer (e.g., x), air blower.

necessary to monitor peroxide and water concentration as long as the carrier gas flow and liquid peroxide injection rate are held constant.

In conclusion, hydrogen peroxide in the vapor phase offers an effective, controllable, fast, and safe means of decontaminating surfaces within a closed chamber of any size. Correct control of decontamination cycles is important to ensure that optimal and safe cycles are used for validated, repeatable applications.

References

1. Akers, J.E., Agalloco J.P., Kennedy C.M., "Experience in the Design and Use of Isolator Systems for Sterility Testing," *PDA J Pharm Sci Technol.*, 1995, 49(3):140-4.
2. Klapes, N.A., and D. Vesley, "Vapor-Phase Hydrogen Peroxide as a Surface Decontaminant and Sterilant," *Appl. Environ. Microbiol.*, 1990, 56: 503-506.
3. Krause, J., G. McDonnell, and H. Riedesel, "Biodecontamination of Animal Rooms and Heat-Sensitive Equipment with Vaporized Hydrogen Peroxide," *Contemp. Topics Lab Anim Sci.*, 2001, 40: 18-21.
4. McDonnell, G., and Russell, A.D., "Antiseptics and Disinfectants: Activity, Action, and Resistance," *Clin. Microbiol. Rev.*, 1999, 12: 147-179.
5. Schumb, W.C., *Hydrogen Peroxide*, monograph series, American Chemical Society, Reinhold Pub. Corp., 1955
6. Block, S.S., 1991. Peroxygen Compounds. p. 167-181. In S.S. Block (ed.). *Disinfection, Sterilization, and Preservation*. 4th ed. Lea and Febiger, Philadelphia, PA.
7. Davis, Jr., N.S. and J. Keefe, Jr., *J. Am. Rocket Society*, p. 63, March-April 1952 Buffalo.
8. Scatchard, G., G. Kavanagh, and L. Ticknor, J., *Am. Chem. Soc.*, 74, 3715, 1952.
9. Pitzer, K. and L. Brewer, *Thermodynamics*, McGraw Hill, 1961, Chapter 16 - 20.
10. Day, R. and A. Underwood, *Quantitative Analysis*, McGraw Hill, 1961, chapter 14.
11. Adams, D., G. Brown, C. Fritz, and T. Todd, "Calibration of a Near-Infrared (NIR) H₂O₂ Vapor Monitor," *Pharmaceutical Engineering*, Vol. 18, No. 4, 1998, p. 66-82.
12. Electrochemical Co., "Engineering Materials for Use with 90% Hydrogen Peroxide," Part 1, 1 December 1950.

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This article discusses the basics of Automated Loading and Unloading Systems (ALUS), including the differences between fixed and flexible systems, as well as covers the evolution of the technology, challenges associated with the use of such systems, industry growth, and recent technology trends.

Automated Loading and Unloading Systems for Lyophilizers

by Peter Heyman

Introduction

In recent years, significant focus has been placed on the development and continuous improvement of fully Automated Loading and Unloading Systems (ALUS) for lyophilizers since their introduction in the late 1980s. Steady increases in targeted sterility assurance level, industry adoption of barrier isolation technology, and the need for potent product containment have driven this evolution. Both fixed and flexible loading systems have been tailored to meet manufacturing requirements, and the lyophilizers themselves have been upgraded to properly interface with these systems.

Reasons for Installing an ALUS

The two primary motivating factors for incor-

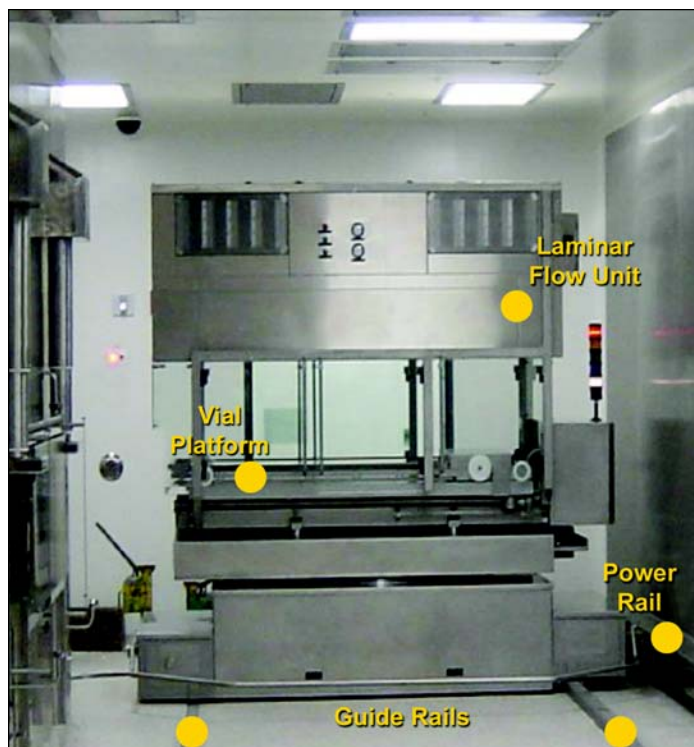
porating an ALUS on a filling/lyophilization line relate to product and operator protection.

Considerable energy has been expended over recent years in achieving higher and higher levels of product sterility assurance, through the use of steam-in-place, closed tank and piping systems, in-line final sterile filtration, automated checkweighing, and the separation of operators from the filling process using Restricted Access Barrier Systems (RABS) and isolators.

As the vials to be processed are only partially stoppered, the product inside the vials is exposed to the external environment in the lyophilizer aisle during transfer to and loading into the freeze dryer. In the traditional process, operators hand carry individual trays with filled vials to the lyophilizer or load trays onto a cart

which is then moved to the chamber. The lyophilizer doors are opened wide, exposing the chamber to the room environment, and the operator loads the trays one-by-one on the (usually) pre-cooled shelves. The operator is in close proximity to the open vials during this transfer, thereby increasing the opportunity for contamination. An ALUS system automates this process, for the most part, removing the operator from the immediate area. An example of one type of ALUS system is shown in Figure 1. With minimal human presence, better control can be achieved over the bioburden in the lyophilizer loading corridor, which can be further enhanced if the loading system is built with its own RABS or isolator protecting the vials throughout the transfer process.

Figure 1. Flexible loading system: transfer cart on rails with dedicated laminar flow.



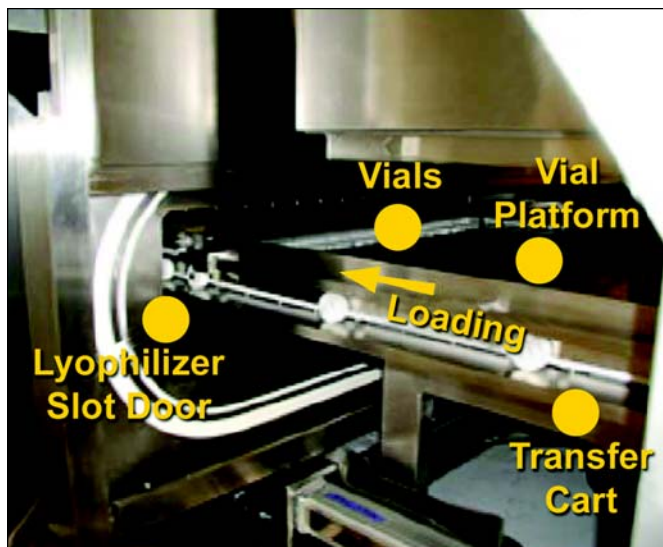


Figure 2. Vial loading through slot door in lyophilizer.

Loading of the lyophilizer through a slot door (also known as “pizza door”) - *Figure 2*, which is either opened intermittently or throughout the loading process, decreases the likelihood of introducing particulate to the interior of the chamber compared to the traditional, full open door scenario. An added benefit is reduced water vapor condensation and frost formation on the cold shelves.

In the case of cytotoxic and other potent entities, an ALUS provides improved operator protection by distancing him or her from the product. This separation can be further enhanced by including a RABS or isolator.

Another benefit of an ALUS is improved manufacturing efficiency through the reduction of personnel in the aseptic core, increased flexibility in timing of loading and unloading of the lyophilizer, and the potential for unloading multiple machines simultaneously.

The size of the lyophilizer corridor may be reduced when using an ALUS (this is project-dependent), and the use of a RABS or isolator should permit the corridor to be designed and operated to a less stringent environmental classification, thereby reducing utility and maintenance costs.

Types of Systems

The first fully automated ALUS were installed in the late 1980s. Since then, approximately 100 ALUS have been made operational, most within the last 10 years, with at least 35 systems being built since 2003. A greater proportion of the units have been placed in the US (~60%) than in Europe (~30%) or Japan (~10%).

ALUS can either be “fixed,” conveyor based and mounted directly at the freeze dryer, or “flexible,” employing a Loading Accumulation Table (LAT) connected to the filling line, a Transfer cart (T-cart) to transport each shelf load of vials to and from multiple lyophilizers, and an Unloading Accumulation Table (UAT) connected by conveyor to a capping machine - *Figure 3*.

Hybrid or mixed systems also have been used with flexible

loading and fixed unloading, or vice versa, typically associated with a pass-through style dryer. Fixed systems are normally selected for operations involving one or two lyophilizers, while flexible systems make more economic sense when using four or more lyophilizers or when considering future expansion. A financial and process flow analysis must be conducted and the facility expansion potential considered when deciding which system to use when three lyophilizers are involved.

A fully automated, flexible loading system, including loading accumulation table, transfer cart, and unloading accumulation table, all with dedicated laminar flow, plus guide rails, power rail, control systems, and operator interfaces can require an investment of roughly \$3 million. However, the value of one or two lyophilizer loads of vials having to be destroyed due to potential contamination by an operator involved in manual loading could far exceed this investment, particularly in the case of high priced biotech products. As an example, a 270 square foot (25 square meter) shelf area freeze dryer holds greater than 77,000 5ml/18mm diameter vials. At a selling price of \$40 per vial, the value of a fully loaded lyophilizer would be \$3 million.

While most flexible loading systems employ floor-mounted rails to precisely guide the transfer cart through the lyophilizer corridor - *Figure 1*, at least one vendor has opted to use laser technology for this purpose. Laser is emitted from the transfer cart and returned by wall-mounted reflectors, providing continuous feedback as to the cart’s precise position within the corridor - *Figure 4*. Such a system obviates the need for guide rails and makes floor cleaning easier. This allows greater flexibility for the addition of new lyophilizers (requiring only a PLC program change) and permits a greater degree of latitude in transfer cart motions. Carts then can be turned through multiple angles and negotiate tight corners, which permits greater choice in room layout. There is less industry history on the performance of these laser-guided carts, and operator traffic in the area must be considered when implementing the system to avoid multiple stops-and-starts of the transfer cart which can lead to greater downtime

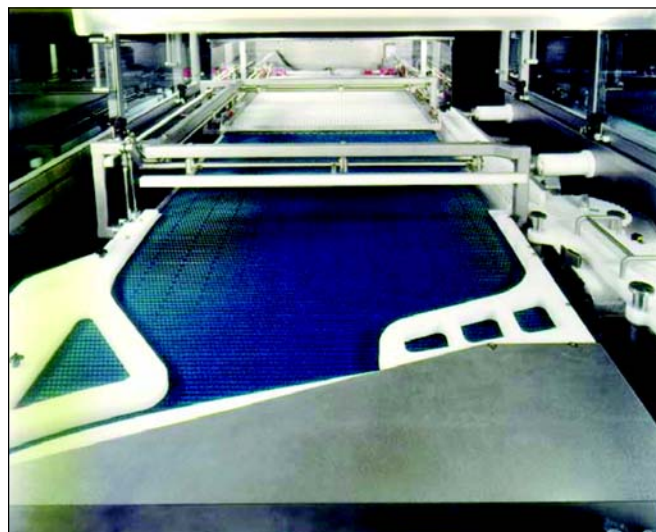


Figure 3. Unloading Accumulation Table (UAT).



Figure 4. Laser-guided transfer cart.

for equipment maintenance.

Power for transfer carts is supplied either through a power rail running parallel to the guide rails and mounted either on the floor or on the wall below the lyophilizer, or from an on-board battery that gets recharged when the T-cart is docked to the loading table, unloading table, or placed in a maintenance position further down the corridor.

Vials can be loaded an entire shelf at a time or one or more rows at a time. A third approach, loading multiple shelves at once, was employed on early installations, but requires a fully open lyophilizer door and long atmospheric exposure time of vial contents while vials are being accumulated, and thus has fallen out of favor. Flexible systems generally load a shelf of vials at once, whereas fixed systems can load row-by-row (or a few rows at a time) or less commonly, shelf-by-shelf. Row loading is best suited for barrier isolation as it presents a much smaller footprint to be enclosed - *Figure 5*. Another

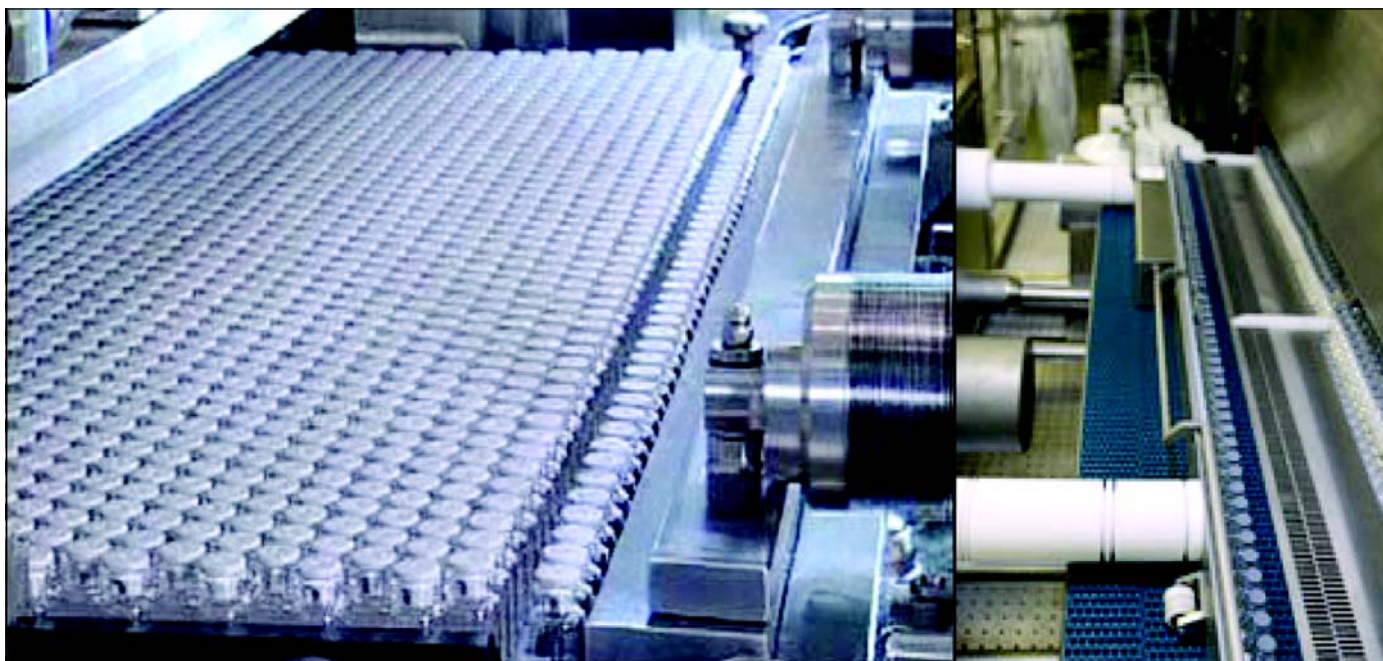


Figure 5. Fixed loading systems with row loading of vials using a push bar.

benefit of fixed row-by-row systems is that the transfer time between filler and pre-cooled shelves is minimized.

Row loading of vials means that the slot door on the lyophilizer must remain open for extended periods of time. To minimize frost formation on pre-cooled shelves, which can complicate vial loading and inhibit heat transfer, some end users have opted to maintain the relative humidity of the loading area as low as 5% RH, and reduce the local temperature to 10 to 12°C versus the normal 15 to 20°C.¹

Roughly 50% of the installed systems are of flexible design, 40% fixed, and 10% hybrid. Of the fixed loading systems, 80% or more load by rows rather than by full shelves.

The decision to go with a pass-through lyophilizer (i.e., front load/rear unload rather than front load and unload) necessitates that the condenser be positioned either to the side of or below the freeze dryer chamber, thereby creating some space restrictions for adjacent process equipment and the potential need for a classified environment on the unloading side.

Most ALUS systems in the field are outfitted with localized, dedicated laminar flow units. Fewer than 20 systems have been built with true barrier isolators - *Figure 6* and a few with RABS. Vendors have seen increasing demand recently for barrier isolated systems, but these still remain a minority of requests.

In addition to an integral laminar flow hood, a RABS includes rigid barriers and often gloveports like an isolator. However, unlike an isolator, some end users permit the doors of a RABS to be opened to clear jams during processing or make other minor interventions with a required subsequent line clearance and manual sanitization step before resuming operation. A secondary laminar flow unit or facility-based laminar flow may be provided on the perimeter of the RABS to compensate for these occasional door openings, including those made during cleaning and set-up between lots.

The doors of an isolator are intended never to be opened during processing. The enclosure is air tight and maintains a desired overpressure, and the interior is automatically sterilized or sanitized via Vaporized Hydrogen Peroxide (VHP) to a desired bio-burden reduction level. In contrast, a RABS is not usually designed to maintain an overpressure and its interior is typically manually sanitized using liquid hydrogen peroxide or other agents.

Challenges

A common issue encountered during the start-up and continuing operation of an ALUS is the alignment of the loading system with the shelves of the lyophilizer. In the case of a flexible ALUS, the transfer cart must align with multiple lyophilizers, each with slightly different chamber and shelf positioning control. Chambers must be carefully positioned upon initial installation, or occasionally repositioned in the case of existing machines being retrofitted with an ALUS, and docking locations must be precisely programmed into the cart's control system.

Features such as linear encoders have been added to the hydraulic cylinder on the shelf control system to more precisely position the shelves relative to the vial transfer plate and loading system. The signal output also may be sent to the transfer cart that may have its own automatic height adjustment system. Clamps may be incorporated on the transfer cart to match up with blocks on the slot door, alignment fixtures may be installed directly on the shelves, and interlocking pins or fingers also have been successfully employed. To compensate for the shelves not being flat or slight misalignments, some transfer plates have been fabricated of thin, flexible 301SS. Through these efforts, the plates can be aligned to within 0.5mm or better, thereby avoiding vial tipping or jamming during the loading or unloading process.

For standard installations not including an ALUS, product temperature is normally monitored over the entire freeze drying cycle by placing thermocouples in vials on different shelves and different areas of each shelf, as the vials are being loaded tray-by-tray into the lyophilizer. Using this information, operators can monitor progress of the cycle, thereby ensuring that product is fully frozen throughout the chamber at the time the primary drying phase is automatically initiated, that product is maintained below its collapse temperature during this drying phase, and that the sublimation process is complete for all vials at the time the secondary drying step is triggered.

In the case of an ALUS-equipped lyophilizer, automatic loading generally precludes placement of thermocouples in vials. Therefore, the monitoring of a production run is limited to observing temperature data coming from the shelf inlet and outlet RTDs and condenser, chamber pressure, and in some cases, automated chamber pressure rise measurements taken at the end of a drying phase. This makes the original freeze drying cycle development/scale-up process and its qualification critical, as well as the lyophilizer control system's ability to carry out consistent, reproducible cycles. Cycle



Figure 6. Transfer cart with barrier isolator.

scale-up work is conducted with the aid of vial thermocouples installed in the lyophilizer solely for this purpose, but not used during production.

A common problem encountered during unloading is the presence of stoppers (and their connected vials) stuck to the underside of the shelf above, originating from the stoppering process at the end of secondary drying when the shelves are compressed with high force onto the stoppers. Factors affecting this adhesion are thought to include the rubber formulation and surface coating, shelf surface geometry, stoppering with partial vacuum in the chamber (leading to a suction effect between stopper and shelf) followed by chamber venting to atmosphere, residual silicone on the shelf and/or stopper, and shelf temperature.

With manual unloading, operators often shake the four-sided stainless steel tray ring back-and-forth until adjacent vials cause the hanging vial to drop down onto the shelf and then unload. With an ALUS, such an action is much more difficult to achieve, thereby resulting in a higher incidence of such vials falling and knocking over adjacent vials while unloading. This has to be addressed by incorporating fallen vial detection/rejection systems at unloading.

Another aspect often overlooked during the detailed design phase is accessibility for cleaning and maintenance of the transfer cart. The cart rails may be positioned close to the wall of the lyophilizer aisle, thereby making access to one side of the cart difficult. Some owners have had the foresight to dedicate a separate section of the corridor for cart maintenance, whereas others have had to install a removable panel in the wall as an afterthought.

One of the justifications used in the past for the costly investment in automating loading and unloading is the complete elimination of operators from the lyophilizer corridor, but this seldom has been realized. In many facilities, an operator still keeps a watchful eye on the process and is available to quickly clear jams and other faults. Optical safety guards are mounted on the sides of transfer carts to prevent collisions with operators and other objects. As the already reliable ALUS systems improve even further, the

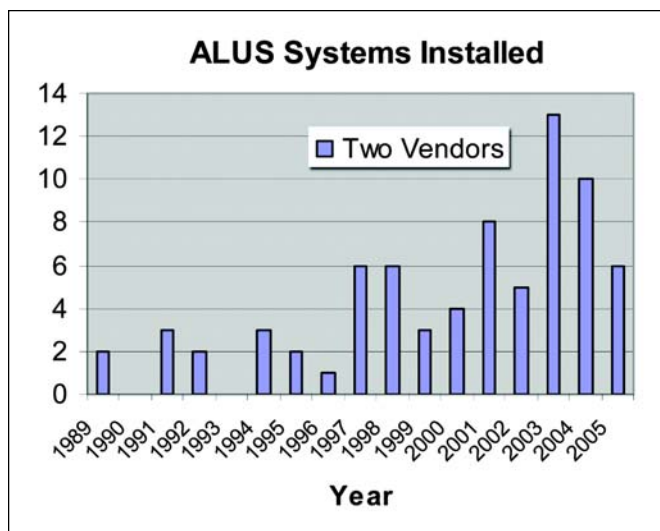


Figure 7. ALUS installations by year.

hope remains that human interventions in the process can be kept to an absolute minimum.

Industry Growth

The overall growth in pharmaceutical company adoption of ALUS systems can be seen in Figure 7. The figure shows the total number of annual installations since 1989 by two of the key industry suppliers. The growth in ALUS lines follows a similar pattern to that of isolators, as published recently by J. Lysfjord and M. Porter in their biannual update,² accelerating in the second half of the 1990s.

Technology Trends

In the future, a variety of ALUS designs will continue to be installed, but at least one equipment supplier is anticipating a reduced demand for shelf-by-shelf loading systems in favor of row-by-row systems.

New features added in recent years to ALUS have included on-board particle counters within transfer carts and wireless Ethernet data transmission, as well as VHP-sterilizable, isolator-enclosed loading carts, and conveyors.

Buffer systems, in which multiple shelf loads of recently unloaded, stoppered vials are stored prior to capping, should find more use as regulatory agency focus grows on the maintenance of sterility of the top of the stopper before enclosure by the aluminum crimp seal.

End users are expected to more clearly designate and define procedures and environmental controls for a technical area for ALUS cleaning and maintenance adjacent to, or part of, the lyophilizer corridor.

Lastly, greater focus will be given to the areas of error prevention, detection, and recovery throughout the process, including provisions for manual backup where warranted.

References


1. "HollisterStier Contract Manufacturing Invests \$5.7 million in Customized Lyophilizer and Facility Upgrade," *Pharmaceutical Online*, 24 May 2004. <http://www.pharmaceuticalonline.com/content/news/article.asp?docid={72f96228-b5bf-4ebe-b4c4-babc57b3005c}>.
2. Lysfjord, J., and M. Porter, "Barrier Isolator Filling Line – Deliveries by Year," presented at the June 2004 ISPE Barrier Isolator Conference, Arlington, VA.

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This article presents an overview of how bacteria can grow and multiply in compendial water systems.

Biofilms – Survival and Growth of Bacteria in Compendial High Purity Water Systems

by Frank Riedewald and Aidan W. Sexton

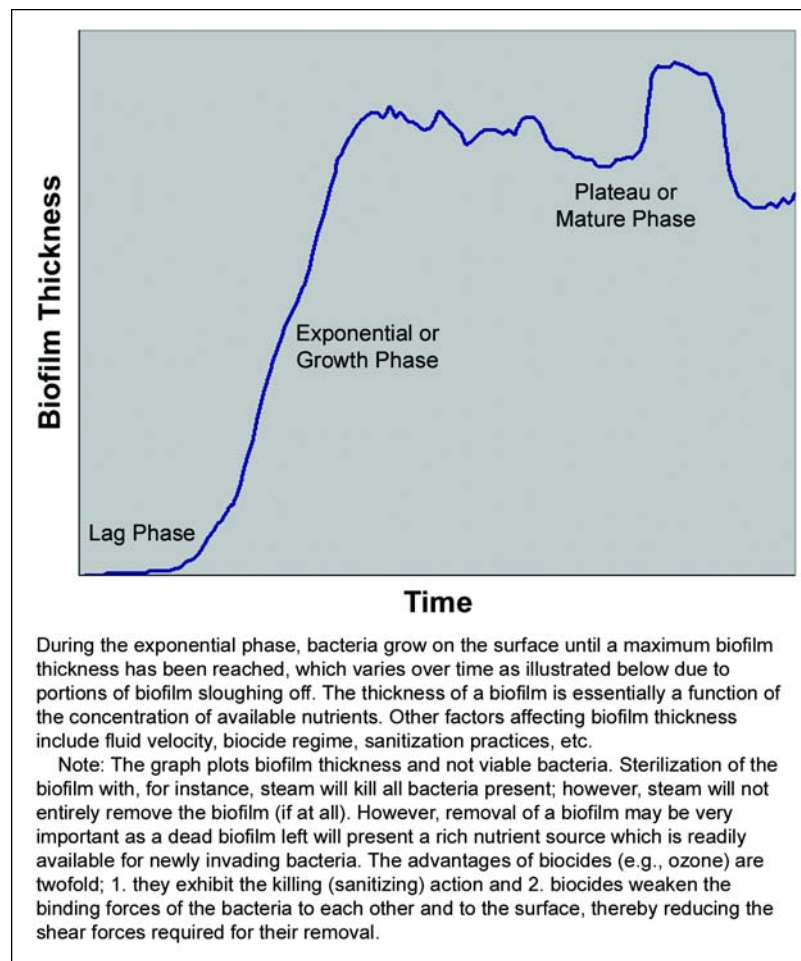
Introduction

The pharmaceutical industry goes to great lengths and expense to control bacterial growth in compendial water systems. Despite all efforts to make it difficult for bacteria to survive in compendial water systems, bacterial survival and growth is observed all too often.

How do bacteria manage to survive and

even multiply in compendial water systems that have been artificially created to be hostile to bacterial growth? Microbiologists have struggled to give a satisfactory answer to this question for quite some time. However, over the last 15 years, it has become more and more evident that bacteria form so called biofilms in high purity water systems. Once bacteria have formed a sessile biofilm on any available surface, their chances of survival and growth increase significantly. In fact, in nature more than 99% of all microbial activity occurs in biofilms, and not as traditionally thought, as free-floating (planktonic) individual bacteria.^{1,2} Kolter has recently commented that “biofilm formation is most likely a universal feature of microbes.”³ The success story of biofilms stretches from the very beginning of life three billion years ago, to today’s tenacious biofilm infections, which constitute about 60% of infections treated by physicians in the first world.^{4,5} This article will first outline how biofilms form in compendial water systems, and then discuss how biofilms will ac-

Figure 1. The three phases of biofilm growth (after Flemming⁶).



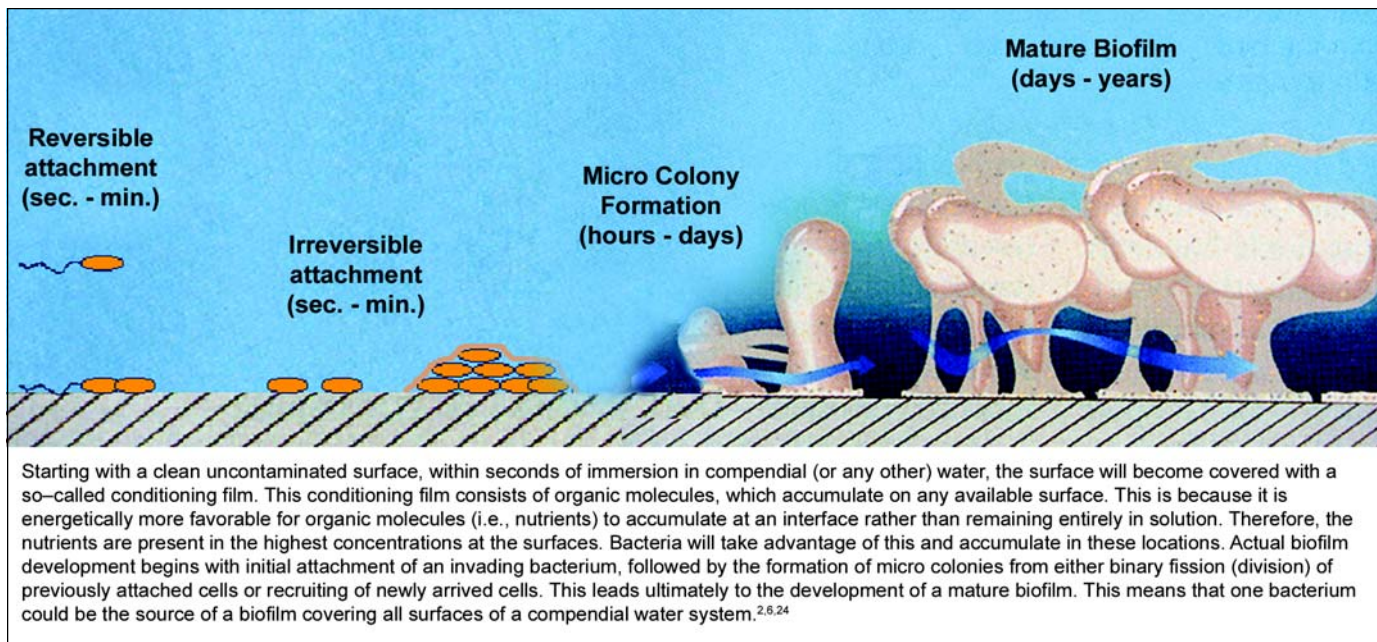


Figure 2. Mechanism and timeframe for formation of a biofilm. (Image adopted after J. W. Costerton and Peg Dirckx, Center for Biofilm Engineering at Montana State University, Bozeman, USA - see Figure 3.)

tively contaminate compendial waters and show that they are the root cause of ongoing bacterial contamination of the water system.

What is a Biofilm?

A biofilm is defined as bacterial cells adherent to each other and/or to surfaces or interfaces and are covered by a slimy substance, which acts as a shield, protecting the biofilm from physical and chemical attack. Planktonic cells on the other hand are free single motile cells in the bulk phase of the water.² The nature of the growth of sessile (non-mobile) bacteria films, while not fully understood, is almost certainly significantly different to planktonic growth. A typical growth curve for a biofilm is shown in Figure 1.

Formation of a Biofilm

Figure 2 illustrates the formation of a biofilm starting from a clean surface, from initial contamination by free floating planktonic cells, to the formation of a mature biofilm, and the approximate time scale involved.

In an aquatic environment, an invading planktonic bacterial cell is attracted to a surface, where it may attach within a short timeframe.^{6,7} Indeed speed of attachment is thought to be a survival strategy of bacteria.⁷ Bacteria that attach first get the best location for survival.

Initial surface attachment is thought to occur through a mechanism whereby the bacteria accumulate at the liquid/pipe (or vessel) interface due to the increased ionic nutrient concentrations that occur at the water/steel interface in high purity water systems.² Since growth conditions are significantly enhanced in this interface zone, biofilm growth is inherently favored over planktonic growth at this location.

The time scale for a biofilm to form depends on a number of factors, such as nutrient availability, hydrodynamics and

substratum characteristics, to name but a few. Since every water system will be different, exact predictions of how long it takes for a biofilm to form is difficult. In a laboratory water system, for instance, an extensive biofilm was found after three months of operation. However, the bulk water quality was always within microbial quality specification.⁸ Thus, a mature biofilm can develop remarkably fast, especially in environments where all requirements for biofilm growth exist, namely:

- an available surface
- a source of water
- initial contamination by an invading planktonic bacterium
- adequate, albeit very low concentrations of nutrients

Once the biofilm has grown to its mature state (Figure 3), a complex collection of micro-colonies, which are protected by a polysaccharide coating, can be observed. The biofilm is interspersed with water channels through which the bulk water flows, transporting nutrients to and waste from the biofilm. Some micro-colonies may be conical in shape, while others may be mushroom shaped.² A further advantage of biofilm formation is that it may allow for enhanced exchange of transmissible genetic information.⁷

The structure of a mature biofilm is not random.² A level of organization can develop in which the cells specialize to achieve a structurally and physiologically complex biofilm.² Bacteria must communicate and coordinate their behavior to achieve a complex biofilm structure as shown in Figure 3,^{7,9} behaving more like an organism, rather than just single bacterial cells. Bacteria are able to sense their environment, process information, and react appropriately.^{7,10} Their ability to sense cell density of other species as well as their own,

communicate with each other, and to behave as a community is called quorum sensing.¹¹⁻¹³ This ability of bacteria, only recently discovered, significantly increases their chances of survival.^{10,13} Planktonic cells on the other hand are not able to communicate with each other, as the chemical signals involved are more likely to be carried away by the bulk water phase without reaching another cell.⁷

Furthermore, the cells composing a biofilm are not simply planktonic cells attached to a surface, as could be deduced from the above definition of a biofilm. Cells, once attached, are demonstrably and profoundly different to their planktonic counterparts.² Their morphology and their phenotype have changed. For instance, a bacterium can only become a productive member of a biofilm community if it refrains from producing a flagellum that might destabilize a biofilm.⁷ These altered cells secrete a polysaccharide substance, which acts both as a protective layer and a nutrient trapping device encasing the biofilm. Different bacterial growth patterns occur, gradually developing a structurally complex mature biofilm.^{2,7}

Within the biofilm, gradients of nutrient, pH, and oxygen exist. In single species biofilms, bacteria alter their gene expression to maximize their survival in their particular microenvironment, while in multi-species biofilms the various bacteria are distributed according to the best requirements of each one.^{7,9} In nature, bacteria usually live in complex mixed species biofilms.^{2,13} However, industrial

Environment	Nutrient Concentration (mg/L)	Growth Mode of Bacteria
Deep Ocean	0.5 – 0.8	Grow in Biofilm only
Distilled Water	Up to 0.5	Grow in Biofilm only
Petri Dish	> 2,000	Grow in Biofilm or as Planktonic cell

Table A. Nutrient levels in different water types.^{2,6,15}

biofilms can be single species biofilms.¹⁴

The image of a biofilm shown in Figure 3 is somewhat idealized. Figures 4 and 5 show a real biofilm in an industrial water system. Hydrodynamics also have an influence on the structure of biofilms. Under the influence of shear stress at higher fluid velocities, biofilms tend to be denser and their surfaces tend to be smoother.¹⁰ In addition, the structures of the biofilm as shown schematically in Figure 3 would become more elongated in the downstream direction¹⁰ influenced by high fluid velocities near the surface.

Nutrient Levels in Purified Water Systems

Although the nutrient concentration in purified water systems is artificially low, bacteria still manage to grow and multiply in these systems. Bacteria can grow and multiply in purified water systems because the nutrient concentration is still not low enough to prevent bacterial growth. In fact, the

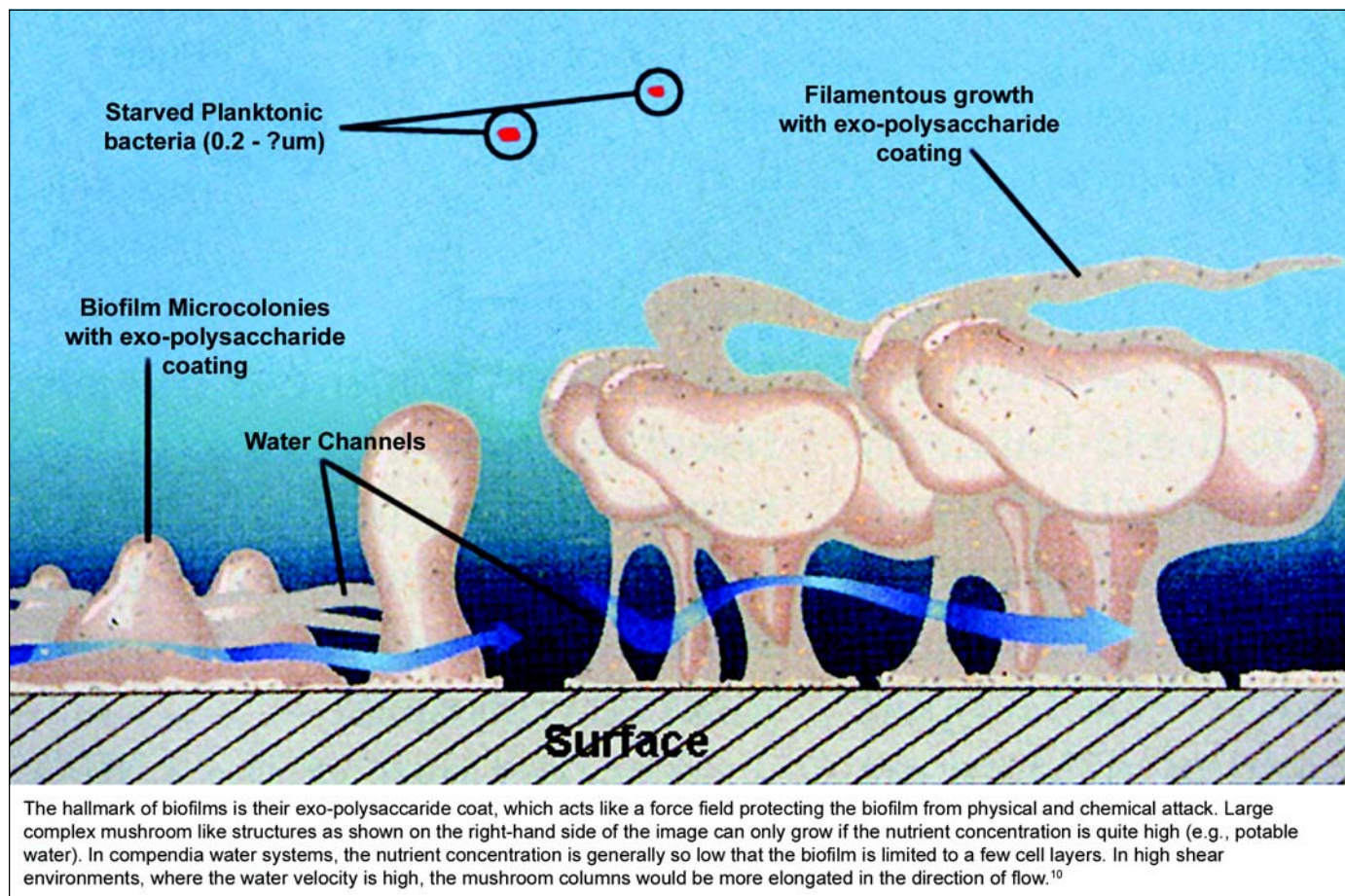


Figure 3. Schematic of mature biofilm. (Image reproduced with permission from J. W. Costerton and Peg Dirckx, Center for Biofilm Engineering at Montana State University, Bozeman, USA.)

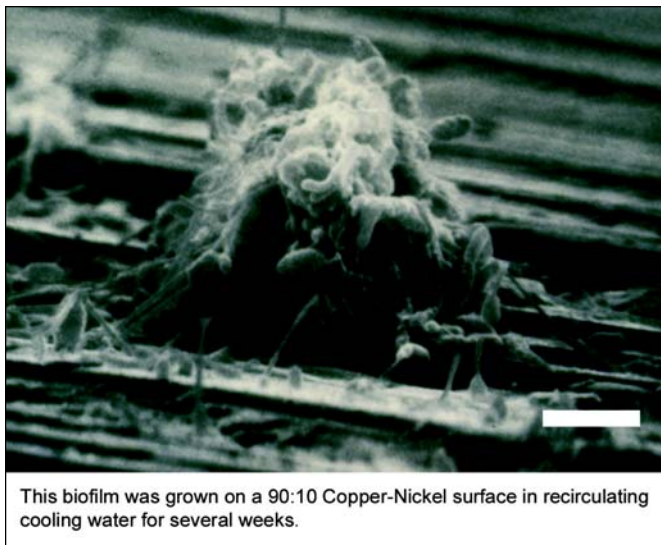


Figure 4. Scanning electron micrograph of a biofilm (Bar 1 μm). (Image reproduced with permission from Rodney Donlan and Donald Gibbon, Center for Disease Control and Prevention, Atlanta, USA.)

nutrient concentration of Deep Ocean waters and distilled waters (Table A) is similar. In both cases, the nutrients are available in infinite quantities, albeit in very low concentrations. The main source of nutrients in compendial water systems is generally the feed water.^{6,24} One should keep in mind that compendial water systems are open systems, meaning that new feed water ensures a constant supply of

Sidebar 1 - The Difficulties of Examining Biofilms

Why have we missed biofilms for so long? This is because they are difficult to study, whereas laboratory work on planktonic cell cultures is easier and more convenient.

At the beginning of the 1980s scientists realized the importance of biofilms in natural and industrial water systems. At this time, direct recovery methods showed unequivocally that more than 99.9% of bacteria in an aquatic system grow in biofilms on surfaces. It took another few years before the complex open structure of biofilms (Figures 3 to 5) came to light and was fully appreciated. Originally, biofilms were thought to be simple mats of bacteria stuck to surfaces. Using a number of techniques in the early 1980s such as the Scanning Electron Microscopy (SEM - Sidebar 2) and the Confocal Laser Scanning Microscope (CLSM - Sidebar 3), the complexity of biofilms was finally revealed.

It is the emphasis placed on laboratory work that has resulted in our missing the significance of biofilms for so long. Only recently have microbiologists realized that in nature, bacteria grow in biofilms and not as single cell culture as studied in the laboratory.² "Microbiologists have been barking up the wrong tree since the time of Pasteur," says Costerton.¹

nutrients, albeit at a very low concentration.

Since the nutrient concentrations found in deep ocean water and distilled water are not significantly different, bacterial growth in distilled waters should be expected, albeit only in a biofilm. Direct microscopic observations have shown that bacteria cannot grow as free floating planktonic cells at nutrient levels found in distilled water systems.¹⁶ However, by forming a biofilm, not alone will these bacteria survive, but they will actually grow and reproduce.^{6,16} Therefore, biofilm bacteria succeed in growing and multiplying in low nutrient environments, which are hostile to the growth of planktonic cells. This is because the food is brought to the sessile bacteria cells in the water system, instead of individual cells wasting energy swimming toward the food.

Bacteria are used to starving conditions. In nature, the bulk of bacterial existence must be spent in starving or slow growing conditions, because no natural environment contains enough nutrients to sustain the voracity of rapid bacterial growth for very long.¹⁷ Paradoxically, these low nutrient concentrations, as found in nature, are actually created by the bacteria themselves.¹⁵ Whenever there is a high nutrient concentration available for bacteria, bacteria move in, multiply, and consume the food source very quickly.

Bacteria can only multiply as planktonic cells if the nutrient concentration is very high. Examples of planktonic cells growing and reproducing can be found in laboratory nutrient rich Petri dishes, bottles of growth media, or inside a host (e.g., human, animal, etc.).^{1,11}

Highly structured biofilms cannot develop if the nutrient concentration is very low. For instance, in Ultrapure Water systems (nutrient concentration < 30 ppb TOC), a biofilm can only develop to a thickness of a couple of cell layers.¹⁸

Why Do Bacteria Grow in Biofilms?

There is insurmountable scientific evidence that bacteria prefer to live in biofilms rather than existing as free-floating planktonic bacteria. Extensive investigations on aquatic systems have shown that in all natural, industrial, and medical ecosystems, biofilm bacteria hugely outweigh their planktonic counterparts in biomass. In nature more than 99% of all microbial activity occurs in biofilms.^{1,2} Since attachment of bacteria to surfaces is so prevalent, it is seen as the most important survival strategy of bacteria in low nutrient waters.^{9,13,19}

Considering all of the advantages that bacteria find in the formation of biofilms, microbiologists now conclude that the preferred mode of bacterial growth is in a biofilm, while the planktonic state is a mechanism for biofilm dissemination or dispersal.²

There are a couple of reasons why bacteria may prefer to live in a biofilm, rather than in the planktonic state. The biofilm is a favorable habitat as it allows access to scarce nutrients. Biofilms provide a defense mechanism against a whole range of stresses, not to understate it; there is strength in numbers.

Favorable Habitat

As already stated, in low nutrient environments, bacteria can only grow while residing in a biofilm. One of the reasons why biofilms are so successful is that they form right where the nutrient concentration is at its highest since nutrients tend to accumulate at surfaces. It is energetically more favorable for organic molecules - nutrients - to be at an interface than remain in solution.² In other words, in low nutrient waters, such as compendial water systems, there is a natural flow of organic materials (i.e., nutrients) from the bulk water phase to the surfaces. By forming a biofilm, bacteria can utilize these surface nutrients.

But the biofilm mode of growth makes the habitat even more favorable. The polysaccharide film encasing the biofilm serves as a nutrient trapping device.² This ability of biofilms to “actively” extract nutrients from the bulk water explains why biofilms can grow in high purity water systems, when their planktonic counterparts starve.² A further advantage for cells in a biofilm is that attached cells, which have died, can be used as nutrient sources by neighboring cells.

Defense

The polysaccharide coating encasing the biofilm also offers a protective shield against physical and chemical attack. Generally, bacteria within biofilms can survive much greater concentrations of biocides (chlorine, penicillin, etc.) than their motile bacterial counterparts in the bulk phase of the water.^{2,19}

Very high concentration and very long exposure times exceeding the recommended concentrations and exposure times of the manufacturers may be required to eradicate biofilms with typical disinfectants as for instance used in the food-processing industry (namely, chlorine, ammonium compounds, iodophores, etc.).²⁰ This is because recommended biocide concentrations and exposure times have been determined by assessing planktonic cell deaths, while ignoring the effect, if any, on the presence of a biofilm.²

One mechanism of biofilm resistance to antimicrobial agents is related to the inability of an antimicrobial agent to penetrate the full depth of a biofilm.²¹ A second theory is that at least some of the cells in a biofilm experience nutrient limitation, and therefore exist in a slow growing or starved state. It is known that starved cells are not very susceptible to many antimicrobial agents.^{19,21}

Protection from heat and drying is also provided by the encasing slime layer, as it is composed of fibrous polysaccharides and contains about 99% water, which protects the biofilm remarkably well from drying,² an important survival strategy as water levels in nature can often fluctuate widely.

Strength in Numbers

As is so often the case, there is strength in numbers. With the advantages of its communal structure, biofilms constitute a protective mode of growth, that allows survival and growth in hostile environments.⁹ Research has shown that bacteria have communication and decision making capabilities, which enable them to coordinate growth, movement, and biochemical activity to achieve:

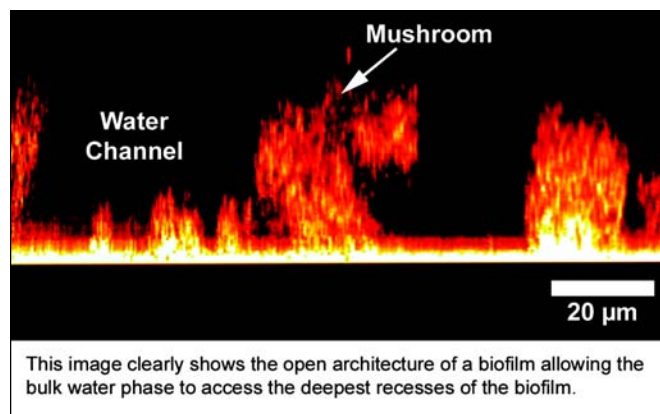


Figure 5. Scanning confocal micrograph of a biofilm in an industrial water system showing the mushroom architecture. (Image reproduced with permission from Paul Stoodley, Center for Biofilm Engineering at Montana State University, Bozeman, USA.)

- Access to resources and niches that cannot be utilized by isolated cells.⁹ For example, bacteria have been found flourishing inside UV disinfectant cells. In nature, many bacteria break down complex organic polymers, requiring the concerted action of many cells.⁹ On the other hand, in laboratory cultures, bacteria are supplied with simple nutrients, which are readily utilized by individual cells.
- Collectively protect against antagonists that eliminate isolated cells⁹ (i.e., protection against biocides, phages, etc.).
- Optimize population survival by differentiation into distinct cell types⁹ (i.e., formation of dormant cells or sub-populations). The resulting genetic diversity, even in single species biofilms, greatly enhances the chances of the biofilm community to survive attack. Diversity will ensure the survival of some bacteria; much in the same way that mixed woodlands survive droughts or insect attacks better than mono-species forests.²²
- DNA exchange between bacterial cells – even with different species – is possible, further increasing the survival abilities of the community.⁷

Contamination of the Bulk Water Phase by Biofilm Bacteria
In high purity water systems, the presence of a biofilm would not be a problem if the bacteria remained only in the biofilm. Unfortunately, biofilms actively contaminate the bulk phase of purified water systems with planktonic bacteria and biofilm cell aggregates. It is these planktonic bacteria and aggregates released from the biofilm, which are detected by typical water quality assessments. In other words, bacterial contamination of the bulk water phase is directly linked to the activity of a pre-existing biofilm. The quality of the bulk water can only be improved by suppressing the biofilm activity below a certain acceptable threshold.⁶

Bacteria living in the sessile community of a biofilm must have a mechanism to colonize new areas, or leave the micro-

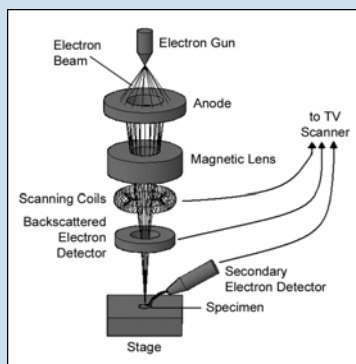
bial community if conditions become unfavorable (i.e., if the area is getting too crowded or nutrients are becoming too limited).⁷ More than one mechanism has been identified by which biofilms spread to other areas or (from our point of view) contaminate the bulk phase of a purified water system

Sidebar 2 - The Principle of the Scanning Electron Microscope

Figure 4 was recorded with a Scanning Electron Microscope (SEM). The SEM is capable of producing high resolution ($< 1\text{ nm}$) images. It allows a greater depth of focus than the optical microscope so it can produce a representation of a three-dimensional sample. Since the SEM operates under vacuum, a biofilm sample must first be dehydrated before imaging. Secondly, as a biofilm is not conductive, it also must be gold plated. Of course, these two processes somewhat alter the biofilm sample.

In SEM, electrons are emitted from a cathode and accelerated toward an anode. The electron beam passes through pairs of scanning coils in the objective lens, which deflect the beam in a raster fashion over a rectangular area of the sample surface. The beam is focused by one or two condenser lenses into a beam with a very fine focal spot sized one to five nm^2 (see image).

Images can be generated from two different electron beams. The first method to generate an image with the SEM is by detecting the backscattered electrons. When the electron beam strikes the sample, some of the electrons will interact with the nuclei of the sample atoms and will bounce back out of the sample without slowing down. This effect is called backscattering. When these backscattered electrons hit the detector, a signal is generated which is used to generate an image. The second method depends on the detection of secondary electrons to generate an image. In this case, the electrons of the atoms of the specimen are pushed by the high velocity electron beam out of the atom and exit the sample surface. These electrons move very slowly, in comparison to backscattered electrons, and since they are negatively charged, they can be attracted to a positively charged detector. This attraction force pulls in electrons from a relatively large area, which is what gives secondary electron images a three-dimensional look, similar to that seen in Figure 4 in the main text.



with bacteria.^{10,19,23} For rippling, detaching, and rolling dispersal (Figure 6), external fluid forces are required. However, no external fluid forces are required for seeding dispersal. The latter mechanism of biofilm cell release to spread to new areas is more sophisticated as the biofilm actively releases single motile planktonic cells. This has been shown to be a programmed set of events leading to a localized hydrolysis of the extra-cellular polysaccharide coating and conversion of a sub-population of cells into motile planktonic cells, which leave the biofilm^{19,23} as indicated in Figure 6.

Conclusion

Biofilms, to date, have been underestimated, both in their extensive occurrence in water systems and their contribution to the overall bioburden in all compendial water systems.^{2,10,14,24} Biofilms in high purity water systems should be seen as normal since currently we neither have the means to prevent a biofilm from forming nor to totally remove biofilms from the surfaces of water distribution systems.⁶

The method of detection of biofilms or their management in high purity water systems is beyond the scope of this article. Overviews are readily available regarding biofilm management strategies for high purity water systems.^{6,25} The following recommendations can be drawn from the literature to minimize biofilm growth:²⁵

- minimization of nutrient concentration in the bulk water phase and thereby at surfaces
- use of disinfectants in high concentrations to kill biofilm cells
- use of mechanical operations to detach biofilms
- selection of materials of the correct smoothness/roughness to make cleaning easier²⁶
- cleaning or removal of the biofilm at short intervals
- drying the system completely whenever possible
- checking the efficiency of countermeasures on surfaces
- use of high water linear velocities throughout the distribution piping

Definitions

Bacteria - Traditionally regarded as single cell entities, bacteria are a very heterogeneous group. The only property they have in common is that they are all prokaryotes. Simply stated, prokaryotes are molecules surrounded by a membrane and cell wall. Prokaryotic cells lack characteristic eukaryotic sub-cellular membrane enclosed "organelles," but may contain membrane systems inside a cell wall.

Typical bacteria: (Eubacteria): Rigid cell walls; unicellular; multiply by binary fission; if motile move using flagella.

Cell - The basic structural unit of living things whether plant, fungus, or animal.

Dissemination - Scattering, distributing over a considerable area.

Metabolism - The sum of all the chemical reactions in a cell.

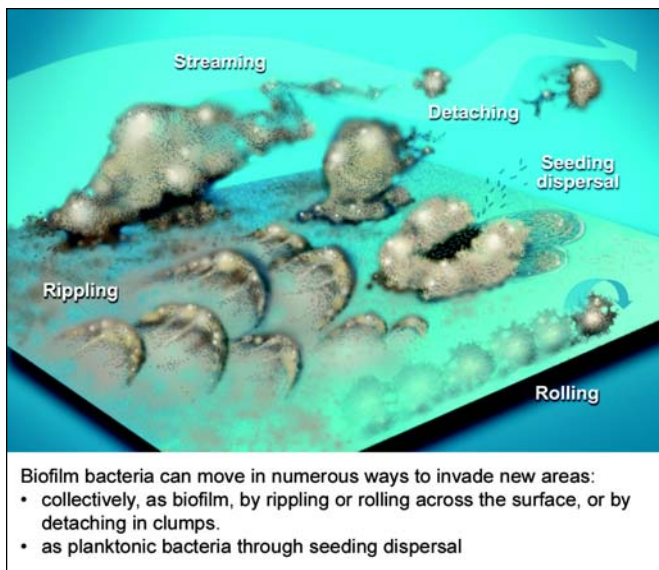


Figure 6. Bacterial dispersal from a biofilm. (Image reproduced with permission from Peg Dirckx, Center for Biofilm Engineering, Montana State University, USA.)

Morphology - The form or shape of a particular organism or structure.

Motile - Having spontaneous, but not conscious or volitional movement.

Polysaccharide - Long chains of monosaccharide (sugar) subunits.

Sessile - Permanently attached or fixed; not normally free-moving.

References

1. Potera, C., "Biofilms Invade Microbiology," *Science*, 27 September 1999, Vol. 273, p. 1795-1797.
2. Costerton, J.W., Lewandowski, Z., Caldwell, D.E., Korber, D.E., and Lappin-Scott, H.M., "Microbial Biofilms," *Annual Review of Microbiology*, 1995, Vol. 49, p. 711-745.
3. Kolter, R., "Surfacing Views of Biofilm Biology (editorial)," *Trends in Microbiology*, Vol. 13, No. 14, 2005, p. 1-2.
4. Nisbet, E.G. and Sleep, N.H., "The Habitat and Nature of Early Life," *Nature*, Vol. 409, 22. February 2001, p. 1083-1091.
5. Fux, C.A., Costerton, J.W., Stewart, P.S., and Stoodley, P., "Survival Strategies of Infectious Biofilms," *Trends in Microbiology*, Vol. 13, No. 14, 2005, p. 34-40.
6. Flemming, H.C., "Biofouling bei Membranprozessen," *Pharma-Technologie Journal*, CONCEPT Heidelberg, 1992.
7. Watnick, P. and Kolter, R., "Biofilm, City of Microbes," *Journal of Bacteriology*, Vol. 182, No. 10, 2000, p. 2675-2679.
8. McFeters, G.A., Broadaway, S.C., Pyle, B.H., and Egozy, Y., "Distribution of Bacteria Within Operating Labora-

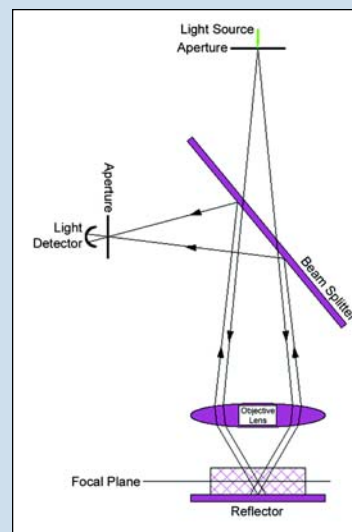
tory Water Purification Systems," *Applied and Environmental Microbiology*, Vol. 59, (1993), p. 1410-1415.

9. Shapiro, J. A., "Thinking about Bacterial Populations as Multicellular Organisms," *Annual Review of Microbiology*, Vol. 52, 1998, p. 81-104.
10. Stoodley, P., Sauer K., Davies D. G., and Costerton J. W., "Biofilms as Complex Differentiated Communities," *Annual Review of Microbiology*, 2002, Vol. 56, p. 187-209.
11. Sauter, K., Camper, A.K., Ehrlich, G.D., Costerton, J.W., and Davies, D.G., "Pseudomonas aeruginosa Displays Multiple Phenotypes during Development as a Biofilm," *Journal of Bacteriology*, Vol. 184, No. 4, 2002, p. 1140-1154.
12. Strauss, E., "A Symphony of Bacterial Voices," *Science*, 21 May 1999, Vol. 284, No. 5418, p. 1302-1304.
13. Jefferson, K.K., "What Drives Bacteria to Produce a Biofilm?," *FEMS Microbiology Letters*, 236, (2004), p. 163-173.
14. Mittelman, M. W., "Biofilm Development in Purified Water Systems," in *Microbial Biofilms*, Lappin-Scott H.M., Costerton J.W., Eds., Cambridge University Press, Cambridge, ISBN 0521 454123, 1995, p 133-147.
15. Morita, R.Y., "Bioavailability of Energy and its Relationship to Growth and Starvation Survival in Nature," *Cana-*

Sidebar 3 - The Principle of Confocal Laser Scanning microscope

Figure 5 was obtained with a Confocal Laser Scanning Microscope (CLSM). With CLSM, 3D images can be recorded without the need to dehydrate or plate samples with a metal. Apart from staining the cells to ensure the cells will fluoresce when hit by the laser beam, the cells can be observed in their natural environment.

The simplest CLSM uses a laser beam and images are taken point-by-point and reconstructed using a computer. The laser beam is focused into a small volume within a fluorescent specimen. Typically, the specimen must be stained in order for it to fluoresce. Only the fluorescent light will be allowed to pass into the detector.



CLSM offers several advantages over conventional optical microscopy, including controllable depth of field, the elimination of image degrading out-of-focus information, and the ability to collect serial optical sections from thick specimens.

- dian Journal of Microbiology*, Vol. 34, (1988), p. 436-441.
16. Warburton, D.W., Austin, J.W., Harrison, B.H., and Sanders, G., "Survival and Recovery of *Escherichia coli* O157:H7 in Inoculated Bottled Water," *Journal of Food Protection*, Vol. 61, No. 8, 1998, p. 948-952.
 17. Chesbro, W., "The Domains of Slow Bacterial Growth," *Canadian Journal of Microbiology*, Vol. 34, 1988, p. 427-435.
 18. Gillis, R.J., "A Comparative Study of Bacterial Attachment to High-Purity Water System Surfaces," *Ultrapure Water*, September 1996, p. 27-32.
 19. Costerton, J.W, Stewart, P.S., and Greenberg E.P., "Bacterial Biofilms: A Common Cause of Persistent Infections," *Science*, 21. May 1999, Vol. 284, p. 1318-1322.
 20. Costerton, J.W., P.S. Stewart, "Battling Biofilms," *Scientific American*, July 2001, p. 74-81.
 21. Lewis, K., "Riddle of Biofilm Resistance," *Antimicrobial Agents and Chemotherapy*, April 2001, p. 99-1007.
 22. Boles, B.R., Thoedel, M, and Singh, P.K. "Self-Generated Diversity Produces 'Insurance Effects' in Biofilm Communities" *Proceedings National Academy of Science*, November 2004, Vol. 101, No. 47, p. 16630-16635.
 23. Hall-Stoodley, L., Stoodley, P., "Biofilm Formation and Dispersal and the Transmission of Human Pathogens," *Trends in Microbiology*, Vol.13, No.1, 2005, p. 7-10.
 24. Flemming, H.C., "Biofouling in Water Systems -Cases, Causes, and Countermeasures," *Applied Microbiology & Biotechnology*, 2002, 59, p. 629-640.
 25. Riedewald, F., "Biofilms in Pharmaceutical Waters," *Pharmaceutical Engineering*, Nov/Dec 1997.
 26. Riedewald, F., "Bacterial Adhesion to Surfaces: The Influence of Surface Roughness," *PDA Journal of Science and Technology*, Vol. 60, No. 3, May-June 2006, p. 164-171.

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This article presents the ability to consolidate various regulated and non-regulated applications onto the same physical server hardware, and discusses how system virtualization works, benefits and limitations, and how to qualify such an infrastructure.

The Use of Virtual Infrastructures in Pharmaceutical Manufacturing

by Adrian Wildangier and Jon Jensen

Introduction

Hardware virtualization is one of the most revolutionary achievements in computer architecture of the past decade. Virtualization provides Information Technology (IT) managers the ability to reliably consolidate multiple servers onto one physical server. This offers significant cost savings since applications can now reside on their own virtual server completely isolated from other applications, while sharing the underlying physical hardware. Additionally, virtualization also provides excellent functionality for disaster recoverability, high availability, and system manageability. The overall picture is a high return on investment and low total cost of ownership of the server infrastruc-

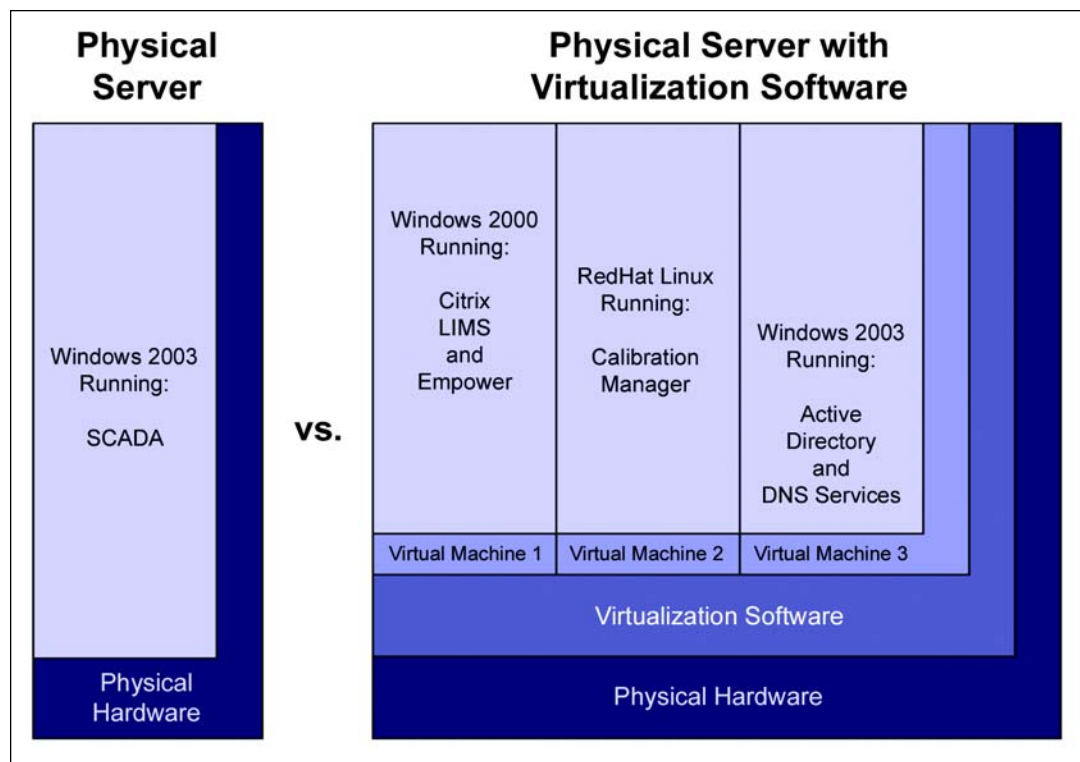
ture. Hardware virtualization is changing the way people look at systems.

The question remains on how to implement this technology in highly regulated industries, where, from a regulatory standpoint, such a paradigm shift can often be met with skepticism and resistance. The purpose of this article is to provide an introduction to virtualization technology, its benefits and uses, and to offer some context to address qualification in the pharmaceutical industry.

Overview of System Virtualization

In the virtual world, physical server components are virtualized and presented to the guest operating system (e.g., Microsoft Windows 2003 or Redhat Linux) as hardware components.

Figure 1. Virtualization software vs. physical server.



Some of these components include the processor, storage media, memory, video card, and network adapter. The guest operating system seems to be communicating directly with the physical hardware, but in fact, it is communicating with virtualized hardware, the virtual machine.

The virtualization software provides each virtual machine access to the physical hardware resources. It then also is responsible for scheduling those resources for each virtual machine. Since the virtual machine does not have direct access to the physical hardware, the virtualization software acts as the bridge between the physical and virtual hardware.

As an example, think of two countries separated by a bridge. The countries regularly trade goods with each other, but neither is allowed to walk over the bridge. For the goods to be passed back and forth, there is a bridge keeper that handles this task. As a trader of the resources, it does not matter who or what is on either side of the bridge, and as a matter of fact, nor does it matter which country the bridge is attached to. The only important aspect is that the bridge keeper has the resources required when they are requested by the trader. In this example, one side of the bridge is the virtual machine asking for the resources, the bridge keeper is the virtualization software acting as the mediator and on the other side of the bridge is the physical hardware providing the resources.

There can be multiple virtual machines that reside on the same physical server without directly impacting or interacting with each other. To understand this scenario, let us expand on the bridge example. Instead of the bridge being a stationary object, think of it as being a rotating bridge. The bridge is not bound to two countries, but instead it can rotate to link to different countries. Every few days the bridge repositions itself so the new country can request from the bridge keeper the resources it needs. As well, each country asking for resources has cement walls, barb wire, and electric fences that prevent any interaction with each other. All interaction has to be

done through the bridge keeper. This is a simplified example, but the rotating bridge manages all the resources scheduling for each country, and the countries' walls represent the isolation between each virtual machine. In reality, the resource scheduling happens very quickly, and depending on the processor, it can happen up to a billion times a second, which gives the impression of a multi-tasking system.

The virtualization software also adds additional complexity when comparing it to a single guest operating system and server. Extra layers create overhead that typically reduce application and guest operating system performance. The trade-off is that with the additional complexity comes enhanced resource management, and the benefits will out-weigh the minimal performance loss.

System Benefits and Uses

With virtualization software, the applications and guest operating system are encapsulated inside a virtual machine which gives an organization additional system benefits. The ability to create virtual machines opens the door to high disaster recoverability, availability, and manageability.

Disaster recovery plans are designed to help IT managers provide business continuity in the event of an organizational disaster. The plan can include information on what restoration processes are required in the loss of an entire datacenter to a single file. When a disaster occurs, the expense involved in providing business continuity can be high. Generally, compatible equipment should be maintained at a standby site for quick recovery. With virtualization, disaster recovery of a virtual machine is simplified.

When restoring a guest operating system in a virtual environment, there are two components that are required. The virtualization software needs to be installed on compatible (i.e., virtualization vendor approved) physical hardware and the virtual machine system files (i.e., configuration and disk files) need to be restored to a location accessible by the virtualization software. Once this is done, the virtual machine can be

turned on without having to reconfigure the guest operating system to properly use the new environment, as it is unaware of any physical changes.

The requirement to install a backup agent on the virtual machine should not be overlooked, but can be mitigated in some instances. Guest operating system backup agents play an important role when specific files need to be recovered from a virtual machine. Backing up the entire virtual machine system files will restore the entire system state of a guest operating system at a specific point in time. While this is useful for disaster recovery purposes, it can be a time consuming process if individual files need to be restored from a guest operating system. The backup agent provides the ability to restore individual files, while a virtual machine is running, mitigating a lengthy restore process. Since backup agents could be an organizational expense, it might be useful to have a cost/benefit discussion to understand which backup strategy would work for each virtual machine. For example, if a virtual machine has a large user community that frequently requests restores, then a backup agent might be useful in this situation. On the other hand, if a virtual machine has a negligible impact on the user community or manufacturing process, then this system could be a good candidate for a virtual machine system file backup.

System restores can be performed on a variety of hardware without impacting the guest operating systems qualification or application validation state. Table A presents organizational benefits of using virtualization software.

Depending on the criteria, the ability to keep a system running during business hours is an important task, especially when high availability is required. In a traditional non-clustered server environment, a system may need to be taken offline for a variety of reasons, some of which include:

- firmware or hardware upgrades
- troubleshooting of physical components
- replacement of system hardware

Organizational Benefit	Explanation
Reduced capital and operational expenses	<ul style="list-style-type: none"> • Less equipment needs to be stored offsite, as multiple virtual machines can be restored on the same physical hardware. • Since virtual machines are not dependent on physical hardware, like-for-like processors (i.e., AMD vs. Intel) or storage controllers (i.e., SCSI vs. HBA) are not required.
Simplified disaster recovery processes	<ul style="list-style-type: none"> • Since the virtual machine hardware environment requires no modification, the qualified state of the guest operating system and validated state of the GxP application does not change. • Depending on the style of backup done, the restore process can be quick and simple to get the entire virtual infrastructure fully functional (e.g., installation of virtualization software and restore of virtual machine configuration and disk files).
Faster business continuity after a disaster	<ul style="list-style-type: none"> • The virtualization software can be installed on a wide range of compatible hardware. • The virtual infrastructure can be pre-installed at a remote disaster recovery site ready for virtual machine restores, as the virtualization software does not have guest operating system or application dependencies, so there is no reconfiguration required to host additional virtual machines.
Less documentation and validation	<ul style="list-style-type: none"> • The installation of additional virtual machines hosting GxP applications does not constitute the re-qualification of the entire virtual infrastructure. • Since the hardware isolation of the virtual machines has been tested and qualified, restored GxP applications only require minimal testing to keep their qualified state (e.g., Confirm the hardware resources are not below a specified threshold). Installation of additional virtualization software and hardware to the virtual infrastructure is done through a subset of qualification tests.

Table A. Organizational benefits of using virtualization software for disaster recovery.

Even in a high availability cluster environment, there may still be the need to take a system offline due to certain software/hardware compatibility issues. In the VMware ESX virtualization infrastructure, there is the ability to migrate virtual machines between physical servers while a guest operating system is running. The affected hardware can then be taken offline during business hours. This technology can eliminate time consuming and expensive server outages. As well, it can reduce the requirement to purchase expensive hardware and license for a high availability environment.

If hardware needs to be upgraded as a result of a system running low on resources, then in a traditional server environment, this could mean a backup and restore, and additional documentation and re-qualification of the new environment. In a qualified virtual environment, there is the ability to migrate virtual machines between physical components, without the complex backup and restoration procedure. Also, the GxP applications and guest operating systems are not impacted. This can mitigate the work required in a traditional server scenario. The only required process is the shut down of the virtual machine, the click of a migration and power-on button. This reduces the time and cost of bringing a new server environment online.

The majority of the virtual infrastructure also can be managed through one central console. The console is flex-

ible enough so that there is the ability to reconfigure or upgrade the processor, memory, network, and disk settings for each of the virtual machines. Since the console only requires network connectivity to the virtualization software, there is the ability to upgrade virtual machines resources at remote locations hence minimizing travel and labor expenses.

The key use of virtualization in the pharmaceutical industry is in maximizing server utilization. This can be particularly applicable for pharmacy companies that do not have the volume of work to justify installing regulated applications on dedicated servers. For example, a QC lab may require a server for a chromatographic data management, laboratory information management, and calibration management system. In a physical environment, each of these applications would require a dedicated server, whereas in a virtual environment, all three applications could be hosted in complete isolation on one physical server. Since there are multiple virtual machines running on one physical host, unwanted costs and tasks can be eliminated. For example, there is a reduction in costs for power, cabling, and management switches.

Virtual Limitations

A business decision must be made when performing server consolidation and capacity planning. Not every server in the datacenter may be a candidate for

virtualization. A virtual infrastructure must be properly sized and configured to obtain optimal system performance. Virtualization overhead needs to be accounted for when installing or migrating servers into a virtual infrastructure. However, existing processor manufacturers are in discussion to include virtualization support for processors, and therefore, virtualization overhead may no longer be an issue by the time of this publication.

When considering the use of a virtual machine, several criteria need to be considered. For each guest operating system required, an organization needs to understand hardware utilization (i.e., disk and processing), amount of concurrent connections (i.e., memory usage per each connection), and any special hardware requirements (i.e., RS232 connections). In this event, a candidate matrix may assist in identifying the most and least suitable systems for virtual infrastructure use or an experienced consultant or vendor.

Since virtualization is about resources consolidation, storage and network strategies need to be addressed. A storage area network or shared high capacity storage solutions are recommended due to their efficiency. The network environment also should be able to handle gigabit Ethernet speeds with potential for link aggregation, such as MAC Address or IP Address load balancing (via the EtherChannel or LACP protocol).

Reduction in Costs

There are immediate cost benefits when running in a virtual environment. First is the ability to consolidate multiple physical server resources. For example, the VMware ESX software has the ability to consolidate 64 physical servers into one virtual environment. With an eight-way server, this may be possible, but it would not be best business practice, since hardware failure on the physical hardware can cause down time for a greater number of virtual machines. Typically, one should stick to the rule of four to six virtual machines per one physical processor (this value may vary depending on the criteria listed in the virtual limitations section and the candidate matrix). A typical medium to enterprise server can cost anywhere from \$10,000 to \$40,000 (all prices shown are for example purposes and will vary with hardware, vendor, and region). If five physical servers are purchased at an average cost of \$25,000 per server, a capital expense of \$125,000 is incurred.

If the same logic is applied to the virtual infrastructure, the only incurred cost is for the physical hardware and the virtualization software license. Each additional virtual machine installation is essentially free (guest operating system and software license and GxP validation costs are not included).³

Virtualization can have an impact

on other externalities that affect the operation and maintenance of a datacenter. Resource consolidation has a domino effect that trickles down to items such as price per network port, KVA UPS power, and BTU HVAC consumption, to even rack real estate, and seismic costs. The overall picture includes significant savings, stream-lined operations, and efficient datacenter management. Virtualization can be an appealing process for all organizations, especially ones that operate under tight budgets.

Overview of Qualification

The need to qualify the virtual environment stems from the intention that the system will be used to host regulated applications. Virtualization software runs directly on the system hardware and exists as a layer between the server hardware and the server operating systems. GAMP 4 categorizes operating systems as a Category 1, and therefore, the functions called upon will be challenged indirectly by the functional testing of the application. However, since virtualization takes place between these two layers, and virtualization software has some distinct functionality of its own, a hybrid approach to qualification is called for. It is worth noting that end users of applications running on virtualized hardware will effectively have no interaction with the virtualization layer.

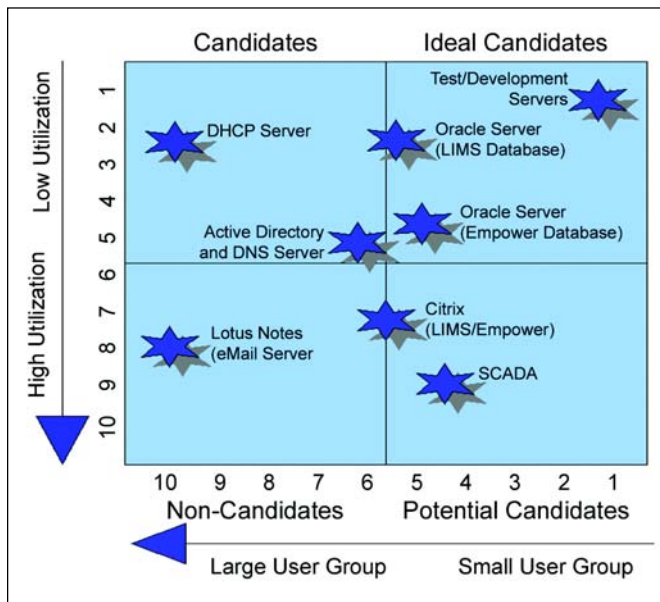


Figure 2. Candidate matrix.

The virtualization software does not provide any viable service to the end user on its own. Once the virtualization software is qualified, a virtual machine can be configured to host a validated application without regulatory impact.

Due to the technical nature of virtualization, the virtual environments are most suitably managed by the IT group and are

qualified as part of the corporate infrastructure. Therefore, User Requirement Specifications (URS) need to be defined by the appropriate network personnel that will be utilizing the functionality. Test cases can then be written based on the URS to test the system.

The first aspect to consider is the hardware itself and the design of a server farm (i.e., cluster). How many servers will be consolidated into a single farm? Which applications and how many users will share the resources of virtualized hardware? These questions will be addressed in the design phase of the project, which will ensure that adequate resources are allocated and all associated system components are compatible. The server configuration will be documented as part of the Installation Qualification (IQ). Each server in the farm will be built with a standardized IQ protocol to ensure that the software is installed properly and functions according to manufacturers' instructions.

Operational Qualification of the virtualization software can now take place. This will include testing of the additional functionality that was defined in the URS. Performing a risk analysis on each URS will clearly illustrate where testing should be focused. For example, one key risk area is the isolation of virtual machines; a test should be performed to verify that the virtual machines created are truly isolated and do not interact with each other. This test may be achieved by "crashing" (i.e., blue screen a Windows server or Kernel panic a Linux server) one or more virtual machines running on the same physical hardware, and verifying that there is no impact to the state of the other virtual machines.

The point at which the end user gets involved in this process is when the regulated application is installed on a virtual system. This, of course, is performed in conjunction with IT personnel that will need to make sure that the specific application is compatible within a virtual environment. Once compatibility has been established, the usual sizing exercises need to be carried out so that appropriate resources

Type of Expense	Equipment	Cost
Capital Costs	1x Physical Server	\$10,000 - \$40,000
Operational Costs (recurring)	1x Hardware Maintenance	\$1,000 - \$2,000 (ea. 2 Yrs)
Maximum Cost Incurred	Average for 1 Server	\$25,000 (1 Time) + \$1,500 (ea. 2 Yrs)
	Average of 5 Servers	\$125,000 (1 Time) + \$7,500 (ea. 2 Yrs)

Table B. The average cost of physical server hardware (all prices shown are for example purposes and will vary with hardware, vendor, and region).

Type of Expense	Equipment	Cost
Capital Costs	1x Physical Server	\$10,000 to \$40,000
	1x Virtualization Software License	\$8,000
	Additional virtual machines (Servers)	\$0
Operational Costs (recurring)	1x Hardware Maintenance	\$1,000 to \$2,000 (ea. 2 Yrs)
	1x Virtualization Software Maintenance	\$3,000 (ea. 2 Yrs)
Maximum Cost Incurred	Average for 5 Servers	\$33,000 (1 Time) + 4,500 (ea. 2 Yrs)

Table C. The average cost of virtualization software with physical server hardware utilizing multiple virtual machines (all prices shown are for example purposes and will vary with hardware, vendor, and region).

can be allocated to the virtual machine build. This can be documented as part of the IQ associated with the application, and once completed, will provide the end user with a qualified environment on which they can perform the Operational and Performance Qualification as part of the overall application validation. As per GAMP 4, the validation will inherently test the underlying operating system, and therefore, any functionality called upon from the virtualization layer as well.

Maintenance of the qualified system must be addressed to ensure that the validated states of the regulated applications are not impacted. Any anticipated changes should be defined in the documentation and guidance should be given on how the impact can affect those changes. A few examples of changes could be the addition or removal of hardware or virtual machines to a physical server. This could even include the allocation of resources to a particular application. These and other changes can be defined within the op-

erational SOP for the virtual infrastructure. By pre-defining various changes and performing some preliminary impact assessments, clear guidance on how to implement changes can be given ranging from formal change control to logbook entries. This will allow for efficient operation and will lessen the chances of costly mistakes. Another key area to address is component compatibility. The operational SOP should contain a list of compatible hardware and supported operating systems to ensure compliance. Setting up monitoring param-

eters for each virtual farm/machine also will allow administrators to proactively stay on top of any performance issues.

Once the Virtual Infrastructure is qualified, it will provide a secure, reliable, and scalable platform that can be efficiently managed to meet not only business demands, but also the increasing regulatory requirements facing the IT industry. There are substantial benefits when configuring applications and guest operating systems in the qualified environment. Some of these benefits provide the ability to consolidate physical server hardware, while increasing resource manageability. This also means a significant savings to the capital and operational budget for the IT department. The initial investment made to set up and qualify a virtual infrastructure will continue to provide excellent long term benefits.

References

1. Silberschatz, A., P. Galvin, and G. Gagne, Operating System Concepts,

2. Tanenbaum, A., Structured Computer Organization, Fourth Edition, 1999, p. 403 - 477.
3. Oblesby, R. and S. Herold, VMware ESX Server Advanced Technical Design Guide, 2005, p. 18 - 263.
4. GAMP® 4, Good Automated Manufacturing Practice (GAMP®) Guide for Validation of Automated Systems, International Society for Pharmaceutical Engineering (ISPE), Fourth Edition, December 2001, www.ispe.org.

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CFR Technologies, Inc., 11-7460 Moffatt Rd., Richmond, B.C., V6Y 3S1 Canada. 

Dr. Gold talks about the challenges of a small company bringing a drug to clinical trials and incorporating advanced manufacturing methods that involve cooperation between manufacturer and equipment vendors.

PHARMACEUTICAL ENGINEERING Interviews

Lynn C. Gold, PhD, Vice President, Research and Process Development, Sonus Pharmaceuticals Inc.

by Cathy Middleberg, Wyeth Vaccines, ISPE Editorial Committee



Dr. Lynn Gold joined Sonus in January 2004 as Vice President of Research and Process Development. She has extensive experience with pharmaceutical development, specifically with the application of emulsion for-

mulations, a major component of Sonus' core technology platform. She oversees discovery research, formulation development, analytical chemistry, manufacturing, and quality control at Sonus. Dr. Gold's previous experience includes 13 years at Fresenius Kabi (formerly Pharmacia and Upjohn) where she had operating responsibility for product and business development activities, including serving as Vice President of Research and Development. She received a BS in chemistry from State University of New York at Buffalo and a PhD from the University of Rochester, New York.

Q Sonus Pharmaceuticals is a small pharmaceutical company that has just reached a milestone in its development as a company with two oncology products in the clinic. Can you give us some background on the company?

A Sonus Pharmaceuticals is a West Coast pharmaceutical company that initiated its first oncology drug candidate development program as it redefined the company in 2000. The company focus is to develop novel drug products that provide better therapeutic alter-

natives for cancer patients and their caregivers. Sonus does this through the people of Sonus who bring this purpose to life by living our values.

Q How does a small company bring a drug to clinical trials?

A Our dedicated group of scientists with a commitment to discovery and quality were the primary ingredient required to get the first idea into the clinic. In addition, a strategic decision outsourcing various aspects of the program that were not feasible for a 50 man company to manage was implemented. The TOCOSOL® Paclitaxel development program has now progressed to a Phase III study. The novel idea of using a vitamin E-based paclitaxel emulsion to reduce problems with a well-known chemotherapeutic, Taxol, is being studied in a metastatic breast cancer trial with more than 800 patients enrolled.

A second oncology drug candidate entered Phase 1 trials in September 2006. This drug candidate is a vitamin E based emulsion formulation (TOCOSOL) of a camptothecin derivative. The goal of the Sonus development programs is to provide safe and easy to use oncology products that add value to the cancer patient.

Q What is unique about TOCOSOL technology?

A One of the many problems encountered in drug development is finding a technique to deliver non-water soluble drug candidates. Vitamin E offers a biocompatible oil that can support incorporation of various drug can-

didates. Typically, these candidates are insoluble in water. Sonus has identified a variety of methods to emulsify vitamin E with various drug candidates for intravenous delivery.

The TOCOSOL emulsion can be aseptically filtered prior to filling, this affords the benefit of not subjecting an oncolytic to terminal heat sterilization. The ability to filter sterilize this emulsion is a result of the high energy process that produces a droplet size distribution of less than 200 nm.

Q Why is this process able to produce a filter sterilizable emulsion?

A One aspect of the system is of course the components of the formulation with the primary excipient being the vitamin E. Some of the physical properties of vitamin E contribute to the overall product quality. In addition, the high energy homogenization process incorporating the proprietary technology from the equipment vendor along with optimization of the process parameters during scale-up contribute to the quality of the product produced and the reproducibility.

Q The FDA is very interested in the advancement of pharmaceutical manufacturing methods. What collaborative processes did Sonus embark on to develop your process?

A The first batches of TOCOSOL Paclitaxel were manufactured at the 2L scale. The homogenization pro-



The Sonus Team.

cess was successfully transferred and scaled up at a Contract Manufacturing Organization (CMO) to 50L. This scale up required cooperation between multiple parties to reduce this to practice for the first time and has been reproduced multiple times. Sonus has demonstrated that this emulsion can be manufactured under cGMPs at commercial scale.

Q How has working closely with the equipment manufacturer made an impact on the process?

A The process is a system built of equipment supplied by multiple vendors. Sonus was able to work with the vendors of the equipment to make systematic modifications as needed and then study the impact of these changes to identify which changes were critical to product quality and which were not. This would have been a difficult task without the cooperation of all the vendors. The modifications ranged from making the

system more pharmaceutically compatible and more end user friendly to making the process more efficient.


Q How will Sonus measure the success of the manufacturing program?

A Quality and regulatory release of the validation batches that will be manufactured to support the commercial scale with a cost effective and reproducible process will mean that Sonus has succeeded with the TOCOSOL Paclitaxel Injectable emulsion manufacturing portion of the CMC.

Q Where is Sonus with the manufacturing program for the TOCOSOL Camptothecin drug product, which is in Phase 1?

A The manufacturing process is in the early development stages, but has the benefit of building on the knowledge base of TOCOSOL Paclitaxel Injectable emulsion. There will be changes to the program as we move forward, but there is a higher level of confidence that this process will be robust and commercializable based on the development history in the company.

Q Does Sonus plan to pursue other therapeutic areas with the TOCOSOL technology?

A Research and development at Sonus is still focused on applications of TOCOSOL technology in the oncology area. Sonus continues to expand its expertise in this technology and will evaluate other therapeutic areas as time and resources permit. 

About Sonus Pharmaceuticals, Inc.

Headquartered near Seattle, Sonus Pharmaceuticals is focused on the development of drugs that provide better therapeutic alternatives for cancer patients, including improved efficacy, safety and tolerability, and are more convenient to use. The Company's lead product candidate is TOCOSOL Paclitaxel, a ready-to-use, injectable formulation of the widely prescribed anti-cancer drug, paclitaxel. In Phase 2 clinical trials, TOCOSOL Paclitaxel has demonstrated encouraging safety and anti-tumor activity in patients with breast, ovarian, lung and bladder cancers. TOCOSOL Paclitaxel is currently in a Phase 3 pivotal trial in patients with metastatic breast cancer. Patient enrollment in the trial was completed in November 2006. Submission of the TOCOSOL Paclitaxel New Drug Application is targeted for the end of 2007. In October 2005, the Company announced the signing of a development and commercialization agreement for TOCOSOL Paclitaxel with Schering AG. Sonus moved its second oncology product candidate, TOCOSOL Camptothecin (SN2310) Injectable Emulsion, into clinical development at the end of the third quarter of 2006. SN2310 Injectable Emulsion is a novel camptothecin compound formulated with the Company's proprietary TOCOSOL technology.

This article discusses how the use of thin-cake vertical candle filters and horizontal pressure plate filters can efficiently remove activated carbon, metal catalysts, and trace insolubles from Active Pharmaceutical Ingredient (API) slurries.

Thin-Cake Filtration Technologies for Removing Activated Carbon, Catalysts, and other Trace Solids from Active Pharmaceutical Ingredient (API) Slurries

by Barry A. Perlmutter

Introduction

As the pharmaceutical industry has changed and grown since the mid-1980s, there are increasing concerns about the safe handling of Active Pharmaceutical Ingredients (APIs). To meet lower exposure limits of unknown compounds and to have batch-to-batch integrity with less operator interaction, the industry's need for new technologies has expanded.

In the chemical synthesis operations of a pharmaceutical plant, the components include

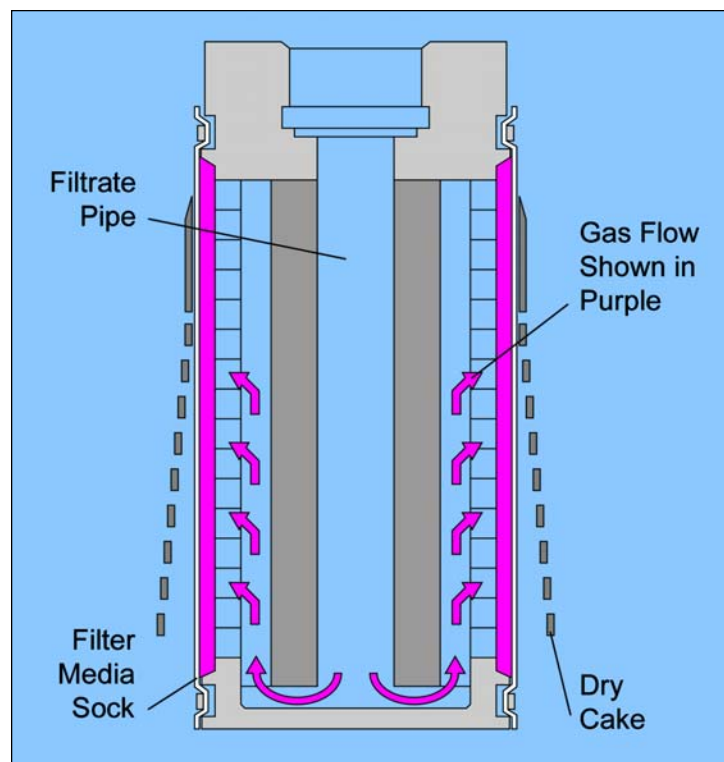
reactors, separation equipment, drying equipment, containment systems, and other process systems and utilities. The reaction step generally includes hydrogenation catalysts, activated carbon, and other accelerators for the precipitation reaction. After this step, separation is required to remove these substances along with unreacted materials, process impurities and reaction by-products, and API residuals.

This article focuses on one area of importance, which is the efficient removal of activated carbon, metal catalysts, and trace insol-

ubles, such as diatomaceous earth, from API slurries. Currently, most API slurries are clarified with the use of manual plate filters, filter presses, bag filters, cartridge filters, and other conventional filter equipment. All of these units require manual operations for cake discharge and cleaning between batches or campaigns, as well as suffer from high labor and maintenance costs, high disposal costs, and the exposure of the operators and the environment to toxic and hazardous solvents and solids in addition to used and contaminated filter cloth, bag filters, and filter cartridges.

Spinning disk filters also are commonly used for clarification. While these units over-

Figure 1. BHS candle showing gas flow to expand the filter media sock for cake discharge.



come some of the special handling requirements of manual filters, they add mechanical complexity to the process as well as special cleaning requirements. Spinning disk filters require drive motors, gear box assemblies (including gear box housing, gear reducers, bearings, shaft bearing arrangement, and bushings, torque loadings, etc.), mechanical seals (either single or double with special maintenance and cleaning), and unique installation concerns, such as center of gravity due to the spinning plates, static and dynamic balancing, and bearing lubrication and design to ensure no exposed threads and cleanability issues and overall maintenance of these components.

This article discusses the use of thin-cake vertical candle filters and horizontal pressure plate filters as alternatives to spinning disk, manual, and conventional filter equipment. These new technologies are currently installed in many API applications and processes. The selection process as well as the technologies are described in the article. The article includes test data and case histories and concludes with a discussion of clean-in-place operations and current Good Manufacturing Practices (cGMPs) guidelines. ANSI/ISA S88 (and IEC 61512-1 in the international arena) batch process control system standards also are examined for validation. Finally, factory and site acceptance testing is described.

Clarification of Slurries and Recovery of Solids

Candle filters and pressure plate filters are installed for clarification and recovery applications from liquids with low solids content. The candle filters are vertical candles, while the pressure plate filters are horizontal plates. The cake structure as well as the process parameters determine the optimum thin-cake technology.

Description and Operation of the Candle Filter

Candle filters provide for thin-cake pressure filtration, cake washing, drying, reslurry, and automatic discharge, as well as heel filtration in an enclosed, pressure vessel. Units are available from 0.17 m² up to 100 m² of filter area per vessel.

Filter Candles and Media

The filter candles (Figure 1) consist of three components: single-piece dip pipe for filtrates and gas, perforated core with outer support tie rods, and filter sock media. The filtrate pipe is the full length of the candle and ensures high liquid flow, as well as maximum distribution of the gas during cake discharge. The perforated core can be a synthetic material, stainless steel, or higher alloys and is designed for the full pressure of the vessel. The outer support tie rods provide for an annular space between the media and the core for a low pressure drop operation and efficient gas expansion of the filter media sock for cake discharge. Finally, the filter media is a synthetic type with a clean removal efficiency to less than one to three microns. As the cake builds up, removal efficiencies improve to less than one micron.

Filter Vessel and Candle Registers

The candle filter vessel is constructed of stainless steel or

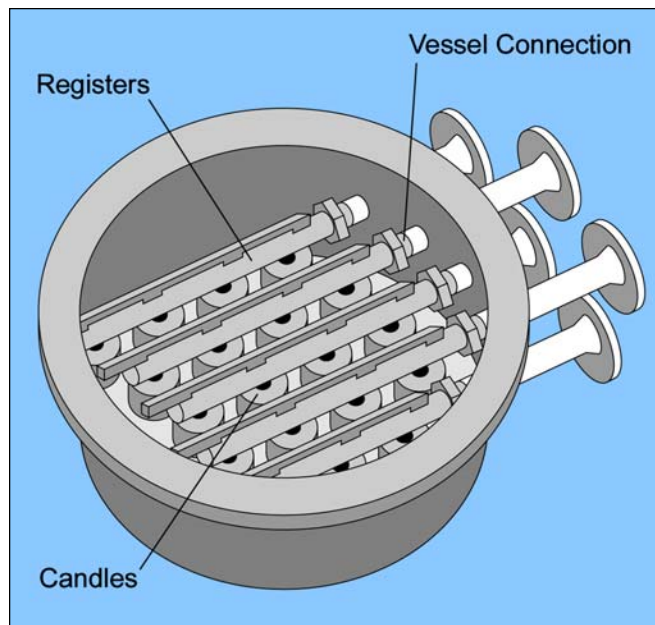


Figure 2. BHS candle filter.

higher alloys. Within the vessel are horizontal manifolds called candle registers. Each candle is connected to a register with a positive seal to prevent bypass. Each register may contain from one to 20 candles depending upon the filter size. The registers convey the liquid filtrate in the forward direction as well as the pressure gas in the reverse direction for filter media sock expansion. Each register is controlled with automated valves to ensure optimum flow in both directions. Figure 2 illustrates the candle filter vessel.

Automatic Process Cycles

Filling: The slurry feed enters the bottom of the filter vessel.

Filtration: The slurry is either pumped or pressurized from the reactor into the vessel. Cake will deposit on the outside of the candle; the separated filtrate will flow through the filtrate pipe and the registers. This process continues until one of the following conditions is achieved: maximum pressure drop, maximum cake thickness, minimum flow, or time.

Washing: Displacement washing or recirculation washing.

Drying: Blowing gas, steam, or "shock" drying.

Heel (Falling-Film) Filtration: The liquid remaining in the vessel cone after filtration or washing is completely filtered.

Cake Discharge: Gas flows sequentially through each of the candle registers, down each of the filtrate pipes, and then is distributed by the perforated core. The filter media sock gently expands by the gas flow and pressure allowing for cake discharge - Figure 1. Alternatively, the cake can be discharged as a slurry.

Description and Operation of the Pressure Plate Filter

The pressure plate filter has similar operating characteristics to the candle filter. The filter design is shown in Figure 3.

Automatic Process Cycles

Filling: The slurry feed enters the bottom of the filter vessel.

Filtration: The slurry is pumped under pressure into the vessel or via gas pressure through the reactor. Cake will deposit on the top of the plates. The separated filtrate will flow through the plates to the center main filtrate outlet. This process continues until one of the following conditions is achieved: maximum pressure drop, maximum cake thickness, minimum flow, or time.

Washing: Displacement washing or recirculation washing.

Drying: Blowing gas, steam, or “shock” drying.

Heel Filtration: The liquid remaining in the vessel cone after filtration or washing is completely filtered.

Cake Discharge: As shown in Figure 5 on page 72, the motors on the top of the filter operate at different frequencies and the plates gently vibrate for cake discharge. The plates vibrate in the vertical and horizontal planes and the solids are conveyed in an elliptical pattern to the outside of the vessel. Gas assist helps in the discharge process. There are no rotating plates, gears, or bushings and mechanical seals are not required.

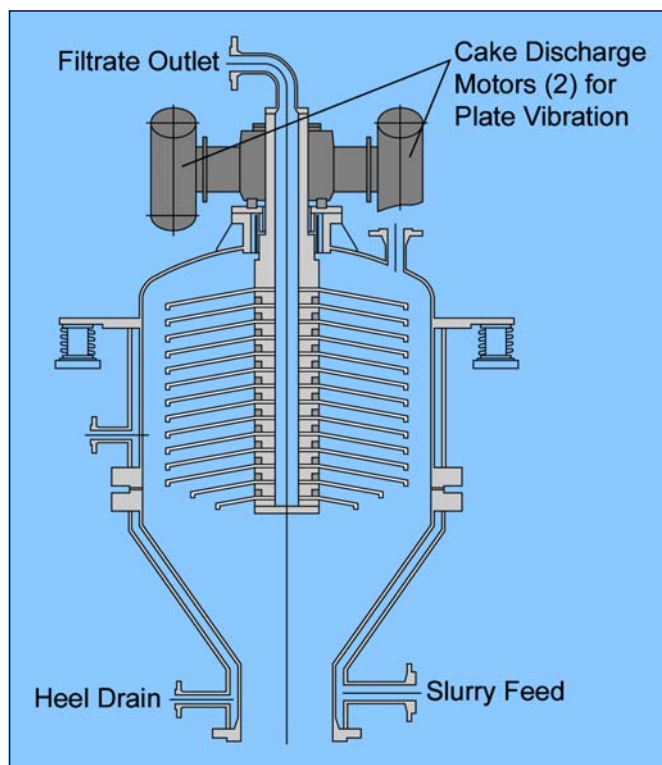


Figure 3. BHS pressure plate filter.

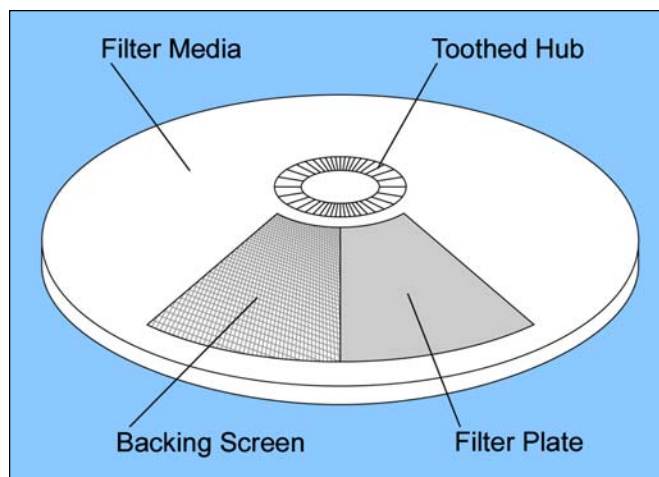


Figure 4. Filter plate.

Selection of Candle versus Pressure Plate Filter Technologies: Cake Structure and Process Parameters

The major difference between the two technologies depends on the cake structure that is formed. Some cakes are better handled in the horizontal and some in the vertical.

Cake Thickness and Filtration: The candle filter is limited to cake structures that can be formed to about five-20 mm. The pressure plate filter can handle cakes up to 75 mm. Both units can conduct filtration up to 150 psig.

Filter Media: The candle filter uses only synthetic media with a clean removal efficiency from one to three micron range and finer down to 0.5 microns. The pressure plate filter also can use metal media. For the pressure plate filter, the clean micron range removal efficiency is also one to three microns and finer.

Cake Washing: If the process requires washing to remove the API from the solids, then generally the pressure plate filter is a better alternative. If washing is not as critical, then the candle filter may be the optimum technology for clarification and recovery.

Heel Filtration: The remaining liquid in the vessel (liquid heel) after filtration or washing can be removed from the candle filter or pressure plate filter by circulation, heel filter in the cone of the vessel, or additional heel filter plates in the pressure plate filter.

Cake Drying: The candle filter can produce cakes with approximately 10% moisture. This moisture level depends upon the specific cake, but the moisture lower limit is that moisture just above the cake cracking point. The pressure plate filter can produce bone dry cakes.

Cake Discharge: Both designs can easily discharge most cakes equally with no residual heel.

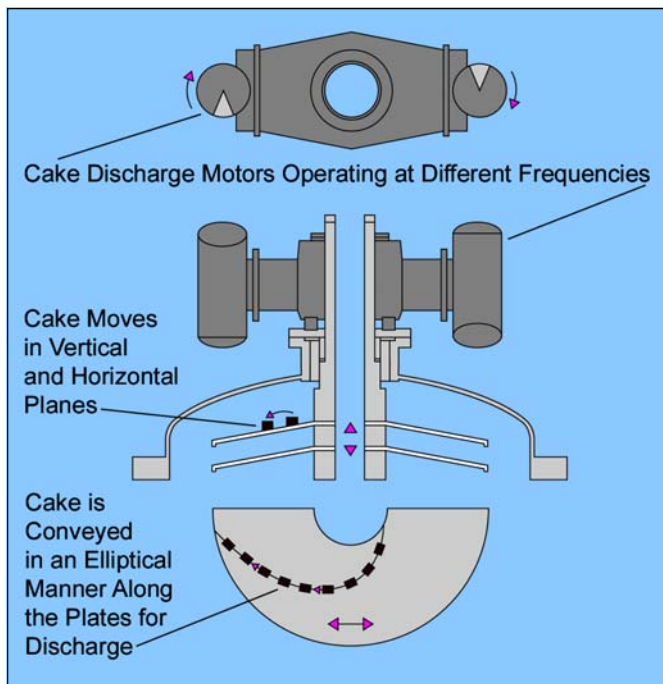


Figure 5. Cake discharge in the pressure plate filter.

Clean-In-Place (CIP)/Steam-In-Place (SIP): Both units conduct CIP/SIP operations in identical manners by filling and circulating cleaning fluids, while blowing gas in the reverse direction to the filtration direction, which creates a turbulent mixture or a quasi-ultrasonic cleaning effect. The pressure plate filter further enhances this operation with plate vibration.

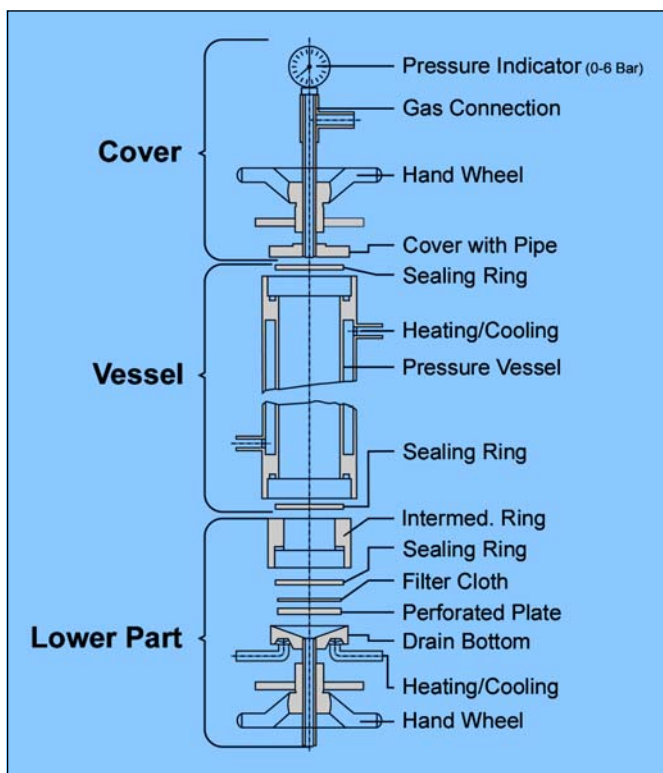


Figure 6. Pocket leaf filter.

Typical Testing to Determine the Optimum Filtration Technology of Vertical Candle Filter or Horizontal Plate Filter

Overview of Bench Top Testing

The bench top testing is conducted using a Pocket Leaf Filter (PLF) - *Figure 6*. The testing will analyze cake depths, operating pressures, filter media, washing and drying efficiencies, and cake discharge (qualitatively, based upon experience of the vendor). The PLF is used to gather the basic filtration, washing, and drying data.

Filtration: The first optimization concerns the cake depth versus the filtration rate. Other parameters that are varied sequentially include cake depth, filtration pressure, and filter media. Cake depths can range between six to 75 mm.

Washing: Displacement washing tests also are performed in the PLF. Washing pressure, time, and wash ratios are optimized to meet final quality specifications.

Drying: Product drying in the PLF is tested by blowing ambient-temperature or hot gas through the cake. The pressure is kept constant and gas throughput is measured versus time.

Example of a Typical Bench Top Testing Program

Bench top tests are conducted on an API/Solids Slurry using a PLF. The tests are conducted to demonstrate that the catalyst and impurities can be removed from the API by filtration. The tests demonstrate that the API can be easily filtered and that thin-cake pressure filtration using a candle filter or pressure plate filter would provide excellent results for this application.

The following filtration options are evaluated and are suitable for this application: candle filter and pressure plate filter.

Test Purposes

The purposes of this test were to:

- Determine if the catalyst and impurities can be separated from an API. The current filtration process is with disposable cartridge and bag filters:
 - A 12,000 liters batch of slurry is filtered in approximately six hours.
 - The slurry contains the catalyst and impurities and is a dark color. The filtrate is the product and should be a clear liquid.
 - The cake is washed and then discharged as a slurry for disposal.
- Determine which type of thin-cake filtration is suitable for this process: candle filter or pressure plate filter.
- Determine the required size for the production equipment.

Test Methods

The Pocket Leaf Filter was used to gather data and make observations on this product. The following information was gathered during this test:

- Filtrate Quality vs. Filter Media
- Filtration Time vs. Feed Volume (Cake Height) and Filtration Pressure
- Cake Height vs. Feed Volume
- Media Blinding vs. Number of Runs

Test Facilities

Tests were performed in a suitable laboratory with original slurry produced by the customer.

Test device: 400 ml Stainless Steel Pocket Leaf Filter with 12 cm² filter area

Filter cloths: FDA-Approved Polypropylene and Teflon cloths

Temperature: - Ambient Slurry
 - Ambient Pocket Leaf Filter
 - Ambient Nitrogen for pressurizing the filter and drying

Test Data – Confidential

Test Results

- Filtrate Quality - The feed slurry is a dark color and the filtrate should be a clear liquid. An FDA-Approved Teflon media produced clear filtrate that contained no visible solids.
- Filtration Time

Filtration Time vs. Feed Volume

The filtration time increased with the square of the feed volume (or the cake height) as expected - *Figure 7*. The data

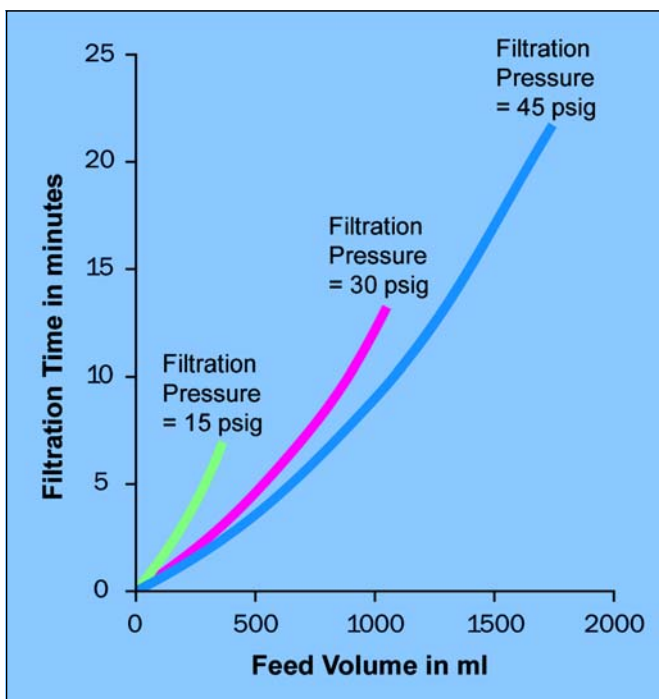


Figure 7. Filtration time versus feed volume.

clearly demonstrate that the filtration time for smaller feed volumes (i.e., thinner cakes) is the preferred filtration method.

The following equation can be used to predict the filtration time based on the data:

Equation 1: $t_F = a + b(V/A_F)^2$, where

t_F = the filtration time in minutes

a = a constant in minutes

b = a constant in minutes * m⁴/m⁶

V = the feed volume in m³

A_F = the area of the filter in m²

A least squares regression of the data yields the following constants for Runs 1, 2, 3, and 4:

	a	b	R2
Run 1, 15 psi	0.32 minutes	27.16 minutes * m ⁴ /m ⁶	0.982
Run 2, 15 psi	0.89 minutes	69.53 minutes * m ⁴ /m ⁶	0.975
Run 3, 30 psi	1.34 minutes	15.75 minutes * m ⁴ /m ⁶	0.983
Run 4, 45 psi	1.72 minutes	9.67 minutes * m ⁴ /m ⁶	0.992

Filtration Time vs. Pressure

The filtration time varied with the inverse of the filtration pressure, indicating that the cake is non-compressible - *Figure 8*. This means that pressure filtration will result in the highest filtration rates and the smallest filter area. The following equation can be used to predict the filtration time for a given amount of feed vs. the filtration pressure:

Equation 2: $t_F = a' + b'/P$, where

t_F = the filtration time in minutes

a' = a constant in minutes

b' = a constant in minutes*psi

P = the filtration pressure in psi

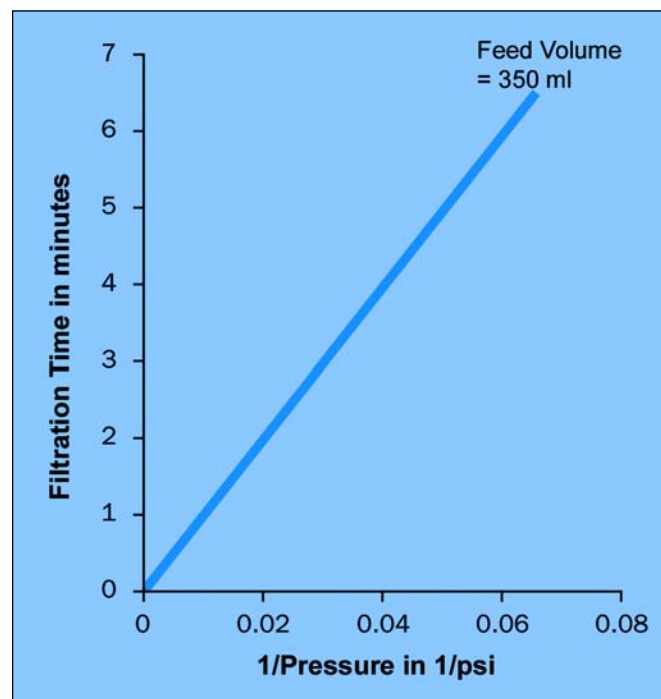


Figure 8. Filtration time versus 1/pressure.

A least squares regression of the data yields the following constants for the filtration time for 350 ml of feed slurry:

	a'	b'	R2
Runs 2, 3, 4	-0.0315 minutes	96.092 minutes * psi	0.992

Cloth Blinding

The same filter cloth was used for each trial and the time required for 400 ml of water to flow through the filter at 15 psi was recorded before the trials and after each run. The flow rate through the media slowed down after the first run, and then reached a steady rate. This indicates that a small and consistent amount of solids remains on the cloth after each run. This result is normal for a cloth media (unlike a cartridge, bag, or paper filter that tends to blind over time due to the particles being trapped in the depth of the filter) and demonstrates that the cloth did not blind during these trials.

Cake Discharge

The cake was discharged dry prior to drying on test Runs 1 to 5, after one minute of drying on Runs six to 10, and as a slurry on Runs 13 to 20. The cake discharge was excellent in each case. This allows the customer to choose the discharge method that is best for their particular situation.

Selection of Production Technologies and Scale-Up

The data indicates that thin-cake pressure filtration is the correct separation method for this product. The result of the tests indicate that either a candle filter or a pressure plate filter are suitable for this application. These filters are batch devices and the cycle time for a batch is the sum of the times for each step in the process.

The actual cycle time for a batch filter is the sum of:

t_{Fill}	= Filling Time	= 5 minutes
$t_{Turbid\ Filtration}$	= Turbid Filtration Time	= NA
t_F	= Filtration Time	= See Each Case Below
t_W	= Washing Time(s)	= 10 minutes
t_{Drain}	= Draining Time	= NA
t_{Drying}	= Drying Time	= NA
t_{Dis}	= Discharge Time	= 5 minutes

t_{Total}	= Total Cycle Time	= Filtration Time + 20 minutes
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Option 1: Process the Entire Reactor Batch in One Drop with a Candle Filter

The cycle time should not exceed six hours (240 minutes) so the allowable filtration time if the entire batch is processed in one batch is 240 minutes - 20 minutes = 220 minutes. The candle filter operates with a typical cake thickness of 10 mm, and Equation 3 can be rearranged to determine the required filtration area to process a 12,000 liter batch.

$$A_F = b'' * V / (h - a'') = 12.846 \text{ mm} * \text{m}^2 / \text{m}^3 * 12 \text{ m}^3 / (10 \text{ mm} - 0.2436 \text{ mm}) = 15.8 \text{ m}^2$$

A Candle Filter with an area of 18.8 m² is the initial choice for this option. We now use Equation 1 and the data from the specific run to confirm that the filtration time in this filter is acceptable:

$$t_F = a + b (V/A_F)^2 = 1.72 \text{ minutes} + 9.67 \text{ minutes} * \text{m}^4 / \text{m}^6 * (12 \text{ m}^3 / 18.8 \text{ m}^2)^2 = 5.7 \text{ minutes.}$$

This filtration time of 5.7 minutes is much less than the 220 minutes allowed, and this confirms that the candle filter is large enough for Option 1. A smaller filter with multiple drops is also possible, but the cGMP requirement is for one complete batch for batch-to-batch integrity.

Option 2: Process the Entire Reactor Batch in One Drop with a BHS Pressure Plate Filter

For this application, the pressure plate filter can operate with a cake thickness of 55 mm (maximum cake thickness = 75 mm) and Equation 3 can be rearranged to determine the required filtration area to process a 12,000 liter batch.

$$A_F = b'' * V / (h - a'') = 12.846 \text{ mm} * \text{m}^2 / \text{m}^3 * 12 \text{ m}^3 / (55 \text{ mm} - 0.2436 \text{ mm}) = 2.82 \text{ m}^2$$

A pressure plate filter with an area of 2.9 m² is the initial choice for this option. We now use Equation 1 and the data from the specific Run to confirm that the filtration time in this filter is acceptable:

$$t_F = a + b (V/A_F)^2 = 1.72 \text{ minutes} + 9.67 \text{ minutes} * \text{m}^4 / \text{m}^6 * (12 \text{ m}^3 / 2.9 \text{ m}^2)^2 = 167 \text{ minutes.}$$

This filtration time of 167 minutes is less than the 220 minutes allowed, and this confirms that the pressure plate filter is the correct size for Option 2.

Summary

The testing demonstrated that thin-cake pressure filtration technologies of candle or pressure plate filters with automatic operations can replace the bag and cartridge filters that are currently being used. The benefits include fully automatic operation, complete containment, no operator involvement, and low maintenance and operating costs. The candle filter requires 19 m² of filter area while the pressure plate filter requires 3 m² of filter area. Further discussion is required of the other process parameters to determine the appropriate choice of technology.

Typical Case Histories

The following are installation process details from candle and pressure plate API applications.

Application 1: Candle Filter with 6 m² of Filter Area

In a recent API installation, the customer installed two candle filters for removing activated carbon and diatomaceous earth from a 3000 kg API slurry. The details are as follows:

- Installation: Duplex candle filters, each with 6 m² of filter area
- Slurry has 25 kg of activated carbon + 15 kg of diatomaceous earth
- Batch size is 3000 kg of an API
- Filtration Pressure = 5 bar
- Drying with nitrogen to 5% final moisture
- Cycle Times:
 - 20 minutes of recirculation of the initial turbid filtrate containing solids. This recirculation was necessary for product clarity
 - 120 minutes of filtration for final production
 - 20 minutes for draining, drying, and cake discharge

Application 2: Candle Filter with 5 m² of Filter Area

- Installation: One candle filter with 5 m² of filter area for de-colorization of an API
- Slurry has 8 Kg activated carbon + 7 Kg of diatomaceous earth.
- Batch size is 4,000 liters of slurry.
- Filtration pressure is 2-6 bar.
- Cycle Times:
 - Filtration = 30 minutes with a cake depth of 20 millimeters
 - Drying = 5 minutes
 - Discharge = 10 minutes
- Process Details:
 - Production results are identical to pocket leaf filter tests of 1200 liters/m²/hour
 - Cake discharge is 100%; no residual heel.

Application 3: Pressure Plate Filter

In this next application, a pressure plate filter was chosen rather than a candle filter. The API is bound to the activated carbon so intense washing is required. The benefit of the vibrating plates allowed the solvent and carbon to mix in the vessel and then reset the bed by filtration. The horizontal plates provided for a well-defined cake structure for cake washing and then bone-dry cake discharge. The details are as follows:

- Installation: Pressure plate filter with 10 m² of filter area
- Slurry has 100 kg of activated carbon.
- Batch size is 6500 kg of an API.
- Filtration Pressure = 3-5 bar.
- Drying with nitrogen to less than 10% final moisture.
- Cycle Times:
 - 4 minutes of recirculation of the initial turbid filtrate containing solids. This recirculation was necessary for product clarity
 - 120 minutes of filtration for final production
 - 20 minutes for draining, drying, and cake discharge

Typical Installation Drawings and P and IDs Candle Filter

The question for API installations generally focuses on containment. Both the candle and pressure plate filters can be

installed in a full glove box or only with a glove box at the cake discharge flange. Figure 9 illustrates a typical full glove box installation for a candle filter.

Pressure Plate Filter

Figure 10 on page 78 illustrates a typical installation where containment is not critical and the cake be discharged into open totes. The polishing filters produce “absolute-rated” final product quality for the downstream operations.

Process Controls and Testing

When evaluating an API application, bench top testing is the first step. After this step, the project continues through various stages until completion. The final step before the new equipment and systems are sent to their final destination is the Factory Acceptance Test (FAT). The FAT may include PLC testing, CIP tests using riboflavin testing, swab tests, and other client specified tests.

Candle filters and pressure plate filters must be controlled either through a local Programmable Logic Controller (PLC) or a Distributed Control System (DCS). For PLC systems, the Batch-S88 standards allows for modular control system operation. It defines the process operations, including the cleaning operations in discrete and individual modules or steps so that operators can perform certain tasks reliably and without variation to ensure a unit that is operated correctly and produces reproducible batches as well as is defined “as clean.” A typical PLC sequence would be as follows:

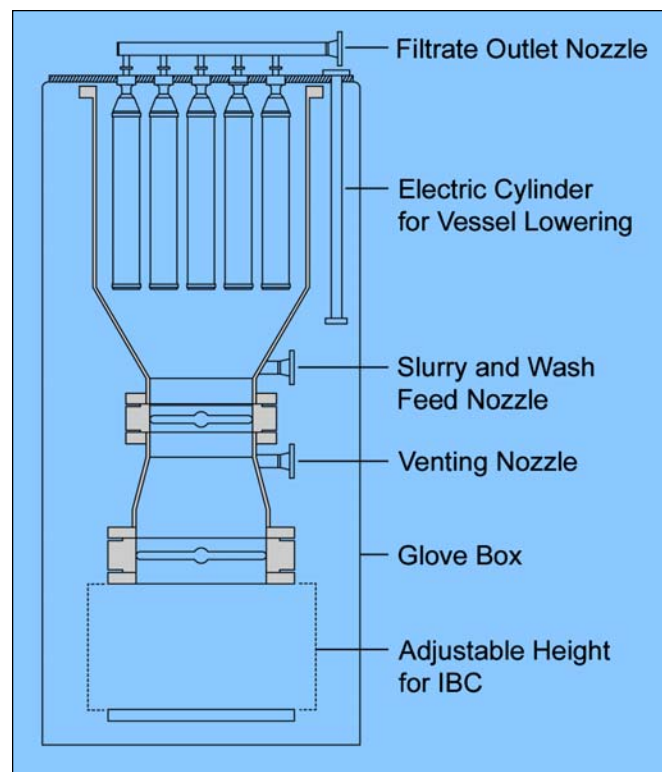


Figure 9. Candle filter with cGMP candles installed in a glove box (not all nozzles are shown; glove box designs require full customization).

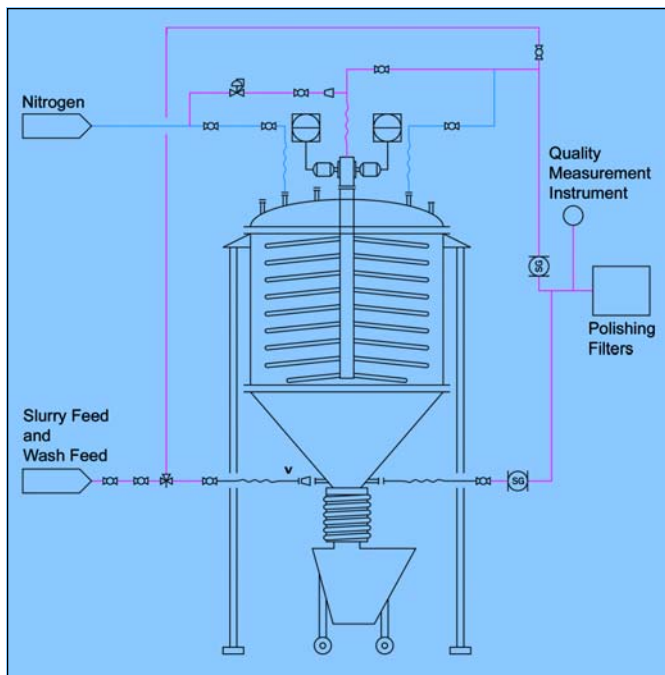


Figure 10. BHS pressure plate filter for cGMP production.

- Idle - in semi-automatic/automatic mode the sequence is not running
- Running - main operation is running without any active sequences
- Typical sequences of operation:
 - Nitrogen purging
 - setup
 - filling
 - wash 1
 - wash 2
 - blowing - drying
 - discharging
 - clean-in-place
- Typical batch outcomes:
 - cycle completed and the sequences begin again
 - aborted and corrective actions are required
 - holding in a sequence and waiting for an action
 - restarting a sequence from a Holding position
 - grounding to put the filter in its fail-safe position at the end of the reactor batch

After successful completion of the FAT, the unit can be shipped. Site acceptance tests as well as the IQ/OQ tests are then conducted using the S-88 standards and formats and repeating the procedures, as necessary.

Summary

Thin-cake filtration operations provide many benefits to the production/clarification process. By selecting the optimum thin-cake technology of candle filter or pressure plate filter, engineers can realize a more efficient process approach, including solids handling and cleaning of equipment with minimal operator involvement for improved safety and environmental concerns.

References


1. Bryan, Sonja, "Cut the FAT: Plan Early to Streamline Your Next Factory Acceptance Test," *Pharma Manufacturing*, (2003): 18-28.
2. Forsyth, Richard J., "Cleaning Validation of Active Pharmaceutical Ingredients," *American Pharmaceutical Outsourcing*, (2006): 16-23.
3. Perlmutter, Barry A., "Test It Right," *Chemical Processing*, (2003): 29-31.
4. Perlmutter, Barry A., "Clean-In-Place Operations for Thin-Cake Filtration Technologies," *PharmaChem*, (2005): 6-9.

About the Author



Barry A. Perlmutter is currently President and Managing Director of BHS-Filtration Inc., a subsidiary of BHS-Sonthofen GmbH. BHS is a manufacturer of thin-cake filtration, washing, and drying technologies. Perlmutter has more than 24 years of technical engineering and business marketing experience in the field of solid-liquid separation,

including filtration and centrifugation and process drying. He has published and lectured extensively worldwide on the theory and applications for the chemical, pharmaceutical, and energy/environmental industries, and has been responsible for introducing many European companies and technologies into the marketplace. Perlmutter began his career with the US Environmental Protection Agency. He received a BS in chemistry from Albany State (NY) University, MS from the School of Engineering at Washington University, St. Louis, and an MBA from the University of Illinois. He serves on the Board of Directors of the American Filtration and Separations Society (AFS) and is a member of ISPE. He can be reached by e-mail at: barry.perlmutter@bhs-filtration.com.

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International

The **International Conference on Harmonisation (ICH)**¹ Steering Committee plus the expert working groups met in Chicago, Illinois from 21 to 26 October 2006. Quality experts from the chemical and biotech areas held Quality Strategy sessions to identify areas to be addressed.

PIC/S

The **Pharmaceutical Inspection Convention and the Pharmaceutical Inspection Cooperation Scheme (PIC/S)**² issued a revision of the PIC/S GMP Guide, which came in to force in August 2006. The revision was made in parallel with the EU GMP guide to include reference to counterfeiting.

Argentina

It has been reported³ that Argentina's regulatory agency, **Anmat**, has published a new regulation dealing with good bioavailability/bioequivalence study practices.

Australia

The following items were added to the **Therapeutic Goods Administration (TGA)** Web site⁴ in October/November 2006:

- TGA news issue 51 November 2006, including an update on the consultation concerning the Australia New Zealand Therapeutic Products Authority (ANZTPA) and details of the release of the next phase of consultation documents on 18 October 2006 with submission to be made by 6 December 2006. Phase III of the Consultation will start in March 2007. Also reported were the changes to the fees and payments, a reminder that medical devices must be transitioned to the new medical device regulatory system prior to 4 October 2007, information that 11 new EU guidelines have been adopted by the TGA since the last issue.
- a listing of Australian Manufacturers licensed to manufacture therapeutic goods
- guidelines on the GMP clearance of overseas medicine manufacturers

- the release of the second phase of consultation on the proposed trans-Tasman regulatory scheme for therapeutic products
- reminder of 2006/2007 annual charges and the installment dates for quarterly payments
- EU guidelines adopted, including Guidelines on the Pharmaceutical Quality of Inhalation and Nasal Products (EMEA/CHMP/QWP/49313/2005)

Canada

Added to the **Health Canada Drugs and Therapeutic Products Directorate (TPD)** Web site⁵ was the Newsletter giving details of a memorandum of understanding that is being developed between the TPD and Australia's TGA to allow for mutual recognition of quality management system certifications for medical device manufacturers in Australia, New Zealand, and Canada to promote regulatory cooperation. Also included were details of a Clinical Trials Manual issued to provide guidance for the filing of a Clinical Trial Application (CTA) in Canada.

Israel

It has been reported⁶ that the Pharmaceutical Administration in Israel has issued a circular in August 2006 relating to accelerated approvals for medicinal products that have already been approved by the US FDA or recommended for approval by the European Medicines Agency (EMA). This applies to medicinal products containing new chemical entities, biological medicinal products, and additional indications to products already registered in Israel.

A guideline has been issued which applied to submissions filed from 1 October 2006 detailing the requirements and the procedure for the approval of brand names for medical products.⁷

Pakistan

A new autonomous regulatory authority is to be established in Pakistan to regulate medicines and medical devices.⁸ This is expected to streamline registration procedures and ensure high quality standards.

Europe

Reported on the Web site for the **European Medicines Agency (EMA)**⁹ in October/November 2006 were:

- the Committee for Medicinal Products for Human Use (CHMP) monthly report¹⁰ from the October 2006 Plenary meeting held 16 to 18 October, and the monthly report from the September meeting held 18 to 21 September 2006¹¹

In view of the anticipated enlargement of the EU with Bulgaria and Romania on 1 January 2007, Marketing Authorization Holders and Applicants are advised that they should provide Modules 1-2 of pending applications to the contact points in the new Member States.

Documents prepared by the Biologics Working Party shown below were adopted at the September CHMP meeting.

- guideline on validation of immunoassay for the detection of antibody to human immunodeficiency virus (Anti-HIV) in plasma pools (CHMP/BWP/298388/2005)
- overview of comments received on draft guideline on validation of immunoassay for the detection of antibody to human immunodeficiency virus (Anti-HIV) in plasma pools (CHMP/BWP/94182/2006)
- guideline on validation of immunoassay for the detection of hepatitis B virus surface antigen (HBsAg) in Plasma Pools (CHMP/BWP/298390/2005)
- overview of comments received on draft guideline on validation of immunoassay for the detection of hepatitis B virus surface antigen (HbsAg) in Plasma Pools (CHMP/BWP/94181/2006)
- Also released for six months review was the Guideline on the Quality of Biological Active substances produced by stable Transgene Expression in Higher Plants (CHMP/BWP/48316/2006).

The CHMP October Plenary meeting held from 16 to 18 October 2006 adopted

the following documents which were released for three months consultation:

- Reflection Paper on Pharmacogenomic Samples, Testing and Data Handling (EMEA/20194/2006)
- Guideline on Excipients in the Dossier for application for Marketing Authorization of a Medicinal Product (CHMP/QWP/396951/2006) (re-released)

The **EMEA** Web site¹² also has been updated with:

- details of the Qualified Person Forum being held on 30 November 2006 in Prague and the ISPE/PDA workshop on 6 to 7 December 2006 on Challenges of Implementing ICH Q8 and Q9
- the CHMP QWP Draft Guideline on Excipients in the Dossier for Application for Marketing Authorization of a Medicinal Product
- details of the Joint CHMP/CVMP Quality Working Party (QWP) Work Program for 2007 including the finalization of the revision of the Note for Guidance on the use of the Near Infrared Spectroscopy (CPMP/QWP/3309/01) to take account of advances in this area
- Guideline on Parametric Release (Veterinary) adopted by CVMP on 12 October 2006 (EMEA/CVMP/QWP/339588/2005)

The **Heads of Agencies**¹³ Web site has been updated with reports from the CMD(h) meetings held 16 to 18 October 2006 and 18 to 19 September 2006.

The CMD(h) also has agreed an updated QRD template for Mutual Recognition and Decentralized Procedures to address in the labeling – information in Braille.

The CMD(h) also has agreed that in exceptional cases it should be possible to validate a decentralized procedure application, where an inspection of sites outside of the EU has not yet been carried out. The manufacturing authorization must be available for the restart of the procedure on Day 106.

A Question and Answer document on the implementation of the new legislation has been provided which outlines practical considerations concerning the phasing in of Directive 2004/27/EC amending Directive 2001/83/EC.

The **European Commission DG Enterprise**¹⁴ Web site has published an up to date list of substances considered as not falling within the scope of Council Regulation (EEC) No 2377/90. Also added was Notice to Applicants Volume 2C – Draft “Guideline on the readability of the label and package leaflet of medicinal products for human use” update 2006. The updates include specific recommendations for blind and partially sighted patients and guidance concerning consultation with target patient groups.

The **European Directorate for the Quality of Medicines (EDQM)**¹⁵ Web site was updated with details of 2007 Proficiency Testing Studies for Official Medicines Control Laboratories and a press release issued following the last Pharmacopoeial Discussion Group Meeting. Five new Ph Eur biological reference preparations also were added. The Certification Procedure section has been updated with two new pages launched for Technical Advice and Inspections. The 2007 technical advice dates also have been added.

Czech Republic

The **State Institute for Drug Control (SUKL)** has published¹⁶ on its Web site: the SUKL Bulletins (9/2006 and 10/2006), including guidelines valid as of 1 November 2006, information for holders of authorization for manufacture of medicinal products and control laboratories, list of medicinal products whose marketing authorization will expire in November and December 2006, VYR-27 Version 1 concerning Application for an authorization/change to authorization for manufacture of medicinal products, and guidance for provision of detailed information on manufacture, including new application forms resulting from amended legislation. Also added were updated lists of distributors and manufacturers.

Denmark

The **Danish Medicines Agency** has added the following to its Web site¹⁷ in October/November 2006:

- Guideline on the Sunset Clause relating to the notification about initiation or cessation of marketing of medicinal products. (According to article 23a of the Directive on medicinal products for human use (2001/83/EC) and article 27a of the Directive on veterinary medicinal products (2001/82/EC)). A new notification form also is available.

Lithuania

The **State Medicines Control Agency** has included on its Web site¹⁸ information for Marketing Authorization Holders concerning the submission of upgraded documentation. According to the Accession Treaty, when Lithuania joined the EU, the transitional period for upgraded Marketing Authorizations ended on 1 January 2007.

Malta

Added to the Web site of the **Medicines Authority in Malta**¹⁹ was updated information concerning fees for Marketing Authorization Applications and Variations which came in to force 6 October 2006.

Also now available on this Web site are Package Leaflets and Summary of Product Characteristics of authorized products.

Netherlands


The Web site of the **Medicines Evaluation Board (MEB)** has been updated²⁰ to include details of an agreement signed between the MEB, the Netherlands Health Care Inspectorate (IGZ) and the US FDA for the exchange of confidential information; the Newsletter for Marketing Authorization Holders and a reminder that annual fees for 2007 are due for all products registered on 1 January 2007. The Medicines Data Bank on the MEB Web site now includes the possibility to search for recently updated package leaflets and Summary of Products Characteristics (SPCs).

Sweden

The **Medical Products Agency** Web site has been updated²¹ on 1 November to confirm that applications for marketing authorizations should be in compliance with current Directives and Regulations implemented in Swedish legislation, including multiple applications or duplicates.

References

1. ICH - <http://www.ich.org/cache/compo/276-254-1.html>
2. PIC/S - <http://www.picscheme.org/index.php>
3. RAJ Pharma, Vol. 17, No. 10, October 2006, p. 660.
4. TGA - <http://www.tga.gov.au/media/index.htm>
5. TPD - http://www.hc-sc.gc.ca/dhp-mps/prodpharma/index_e.html
6. RAJ Pharma, Vol. 17, No. 9, September 2006, p. 608.
7. RAJ Pharma, Vol. 17, No. 10, October 2006, p. 674.
8. RAJ Pharma, Vol. 17, No. 11, November 2006, p. 756.
9. EMEA - <http://www.emea.eu.int/whatsnewp.htm>
10. EMEA/CHMP/410526/2006 - 27 October 2006.
11. EMEA/CHMP/325128/2006 - 29 September 2006.
12. EMEA - <http://www.emea.eu.int/Press%20Office/presshome.htm#>
13. HOA - <http://heads.medagencies.org/>
14. EC - http://ec.europa.eu/enterprise/pharmaceuticals/index_en.htm
15. EDQM - <http://www.pheur.org/>
16. SUKL (Czech) - <http://www.sukl.cz/enindex.htm>
17. DMA - <http://www.dkma.dk/1024/visUKLSArtikel.asp?artikelID=746>
18. SMCA - <http://www.vvkt.lt/engl/>
19. MA - <http://www.medicinesauthority.gov.mt/news&events.htm>
20. MEB-CBG - <http://www.cbg-meb.nl/index.htm>
21. MPA - http://www.lakemedelsverket.se/Tpl/StartPage____395.aspx

This information was provided by Karen Flatt, Pharmaceutical Research Associates (UK). 

Safety Manager System

Honeywell has announced the release of the newest version of its safety instrumented system (SIS), Honeywell Safety Manager Release 110. Safety Manager is a component of the Experion® Process Knowledge System (PKS), Honeywell's process control and automation platform that ties together critical subsystems within a manufacturing facility to give operators a better view of how processes are functioning. The latest version includes new integration capabilities with systems such as process simulation tools and fire and gas detectors, as well as a data exchange and control communication protocol that will allow safety engineers to design and build large integrated and distributed plant-wide safety strategies.

Honeywell International Inc., www.honeywell.com.

Fermentor Feed Pump



Watson-Marlow Bredel, a leading manufacturer of peristaltic pumps, announces its 520 Series dispensing pump for accurate metering, dosing, and transferring of fermentor nutrients in sanitary environments. The pump is ideal for handling huge flow fluctuations where nutrient requirements vary during the organisms' growth profile. The 520 Series accepts eight different tubing materials and sizes up to 9.6mm for flow rates ranging from 4 microliters/min up to 3.5 liters/min and pressures up to 100 psi.

Watson-Marlow Bredel Inc., www.watson-marlow.com.

Pure Water Brochure

A new brochure from Veolia Water Solutions & Technologies provides a concise discussion of water purification in the pharmaceutical industry, and introduces a range of solutions specifically designed to meet, reliably and cost effectively, that industry's

uniquely demanding requirements. Illustrated throughout with photographs and diagrams, the brochure discusses the production of purified water, highly purified water, pyrogen free water and WFI as critical processes, and lists the key standards with which water treatment plants for use in the pharmaceutical industry must comply.

Veolia Water Solutions & Technologies, www.elgaprocesswater.com.

Process Container Film

Millipore Corp. has announced a new multilayer single-use process container film with exceptional clarity and robustness. Disposable manufacturing is an industry trend that offers important advantages, including reduced cleaning and validation requirements, increased flexibility, and lower risk of cross contamination. PureFlex film will enable customers to have better visibility into their process container while also providing enhanced containment of their product.

Millipore Corp., www.millipore.com.

Diagnostics Suite

Emerson Process Management has announced the availability of Advanced Diagnostics on its industry leading Rosemount 3051S Series of Instrumentation for pressure, flow and level solutions using the HART communications protocol. The ASP™ Diagnostics Suite, embedded in Emerson's scalable, highest performing, and most reliable pressure transmitter, provides users with new tools for troubleshooting, detecting, and preventing abnormal situations. Patented statistical process monitoring technology, integral to the transmitter, provides users with an early warning of abnormal process or equipment conditions such as plugged impulse lines, changes in fluid composition, or other events signaled by a change in the noise characteristics of the pressure signal.

Emerson Process Management, www.emersonprocess.com.

Condition Manager

Invensys has introduced a new intelligent real-time condition management component for the company's InFusion

enterprise control system. The InFusion Condition Manager builds upon Invensys' award-winning Avantis.CM technology to provide the ability to collect real-time condition data from an even broader range of plant data sources and to interoperate with the full range of Invensys and third-party applications supported through the InFusion application environment. The InFusion Condition Manager provides powerful tools for analyzing and contextualizing data and applies an expert rule set that first triggers and then manages the appropriate operations, engineering, or maintenance actions.

Invensys plc, www.invensys.com.

Tubing



NewAge Industries has announced the availability of PTFE, FEP, and PFA fluoropolymer tubing (often referred to as Teflon® tubing) in six styles: straight, thin wall, coiled, corrugated, convoluted, and stainless steel over-braided. A large inventory is stocked for applications involving all types of fluid and air transfer, including chemical, pure water, food and beverage, pharmaceuticals, adhesives, medical and laboratory use, robotics, and others. Fluoropolymer tubing is best known for its non-stick properties and heat resistance.

NewAge® Industries Inc., www.newageindustries.com. 

*To submit material for publication in **Pharmaceutical Engineering's** **New Products and Literature** or **Industry and People** departments, e-mail press releases with photos to pharmeng@ispe.org for consideration.*

Extract Technology Name Revived Under New Ownership



The US-based private investment firm, Insight Equity, acquired the Walker Group, resulting in the UK-based manufacturer of pharmaceutical equipment to revert to its former name, Extract Technology Limited. David Pallister has been chosen to lead the company.

Extract Technology, www.extract-technology.com.

GlaxoSmithKline to Acquire Domantis

GlaxoSmithKline (GSK) plc has announced that it has entered into an agreement to acquire Domantis Ltd, a leader in developing the next generation of antibody therapies, for £230 million (US \$454 million) in cash. Domantis, a privately owned company, will become part of GSK's Biopharmaceuticals Centre of Excellence for Drug Discovery while continuing to operate from laboratories in Cambridge, UK. The acquisition agreement is subject to clearance under the Hart-Scott-Rodino Antitrust Improvements Act and is expected to complete in January.

GlaxoSmithKline plc, www.gsk.com.
Domantis Ltd., www.domantis.com.

New Scholarship Program at Sartorius


Sartorius AG has announced its new "Sartorius International Biosciences Scholarship." The scholarship will initially offer ten positions to students of upper semesters, those who have already earned a degree in the natural sciences and/or technology (such as bioprocess engineering, biochemistry or sensorics), and to those who would like to gain experience working at a German technology group. Integrated

into global teams, the scholarship program participants are to work on selected projects in research and development as well as product marketing in the Biotechnology Division.

Sartorius AG, www.sartorius.com.

New Company to Promote London's Genetic Research Capability

London Genetics, a specialist agency created to facilitate partnerships between industry and academic centres of excellence in genetics and genomics-based research across London, was launched 12 December at the Genesis meeting. London Genetics is a unique organization that generates and manages partnerships between leading academic and clinical researchers and the biotech and pharmaceutical industries.

London Genetics, www.londongeneticslimited.co.uk. 

ISPE Student Chapters – Paving the Way for the Society's Future

by Rochelle Runas and Phillip Pursifull

On a February evening in New Jersey in 1992, they broke bread and passed the pasta to celebrate. ISPE's North Jersey Chapter board had just handed 14 students from the New Jersey Institute of Technology a charter certificate inaugurating them as Members of ISPE's first student chapter.

The historic moment marked the beginning of what would later become a Society program that today, boasts more than 40 active Student Chapters across the globe with more than 1,000 Student Members.

Recognizing that students are the future of the industry, one of ISPE's goals is to develop students into competent pharmaceutical professionals and encourage them to pursue pharmaceutical careers. To highlight the efforts and initiatives that are part of this endeavor and to encourage Society

participation, *Pharmaceutical Engineering* will profile active ISPE Student Chapters. The profiles will shine a spotlight on the people behind the scenes who have given and continue to give their time and energy shaping the next generation of industry professionals.

No Such Thing as a Pharmaceutical Engineer

When ISPE Members Joe Manfredi and Bob Lechich first approached the New Jersey Institute of Technology



From left to right: Industry/ISPE Advisor Bob Lechich, Jim Ansbro, Tracey Chodkwisz, Justin Mahalik, Chapter Advisor Demetri Petrides, Brian Huie, Rick Salsa, Larry Perfetto, James Carloni, Richard Lojek, and Steve Wehner at the first student chapter charter ceremony at NJIT in 1992.

(NJIT) with the idea of forming an ISPE Student Chapter, it drew a response that typified the pharmaceutical industry's place in academia at that time. "They looked at me like I had three heads and asked 'What is ISPE?' There was no such thing as a pharmaceutical engineer," said Manfredi.

Manfredi and Jon Tomson, who volunteered to form the second ISPE Student Chapter at Rutgers, The State University of New Jersey, were faced with the challenge of planting a seed where there was no soil. Like many universities at the time, departments of chemical engineering, mechanical engineering, and industrial engineering existed, but not pharmaceutical engineering.

"The colleges did not have a compelling reason to be a part of ISPE," said ISPE Founding Member Jim O'Brien, who has been involved in student development initiatives since their early stages.

"After we began the early Student Chapters, we realized that many universities did not offer courses specifically targeted at the industry, so then we began to work with them to develop curricula," said ISPE Chairman Jane Brown, who helped start-up seven Student Chapters in the Carolina—South Atlantic Chapter (CASA).

The NJIT Student Chapter found

Concludes on page 2.

It's More than Just a Poster

If you attended any of the past few Annual Meetings, it was hard not to miss the sight of students standing nervously in front of their huge poster displays.

The ISPE Student Poster Competition is a high-pressure event where each student gives a five to 10 minute summary of their research, using a detailed poster to illustrate advanced and complex information for the judges. The judges add to the tension by quickly firing questions at the delegates to see how well they know and can communicate their subject matter.

It is common to hear students say that the poster competition does more than help them get real-world feedback from perusing Industry Members.

"I got my job when I was participating in the 2004 poster contest," said Iyad Al-Rabadi. "The vice president of my current company, Austin AECOM, stopped by my poster and asked me to give him a presentation about my poster

without realizing that he was actually interviewing me. After the presentation, he asked me if I would be interested in a position as a process engineer. One month after that, I went to Austin AECOM for an interview after which I got my current job!"





ISPE Student Chapters...

Continued from page 1.

its home in the chemical engineering department in 1992. Not until a decade later did NJIT establish its own pharmaceutical engineering program, Manfredi said.

An Eye Opener

The formation of a Student Chapter is a grassroots effort between a university and local ISPE Affiliate or Chapter. Each Student Chapter is sponsored by a local affiliate or chapter, which along with industry and faculty advisors, provide instrumental development and support.

Currently, there are 41 active Student Chapters, 10 inactive chapters awaiting new leadership, 11 chapters currently under formation, and two with ongoing educational programs. The North American Chapters support the majority of the Student Chapters, with ISPE Affiliates sponsoring eight Student Chapters in Germany, Ireland, Poland, Sweden, United Kingdom, and Singapore. The Singapore Student Chapter comprises students from five universities. The first student activity in France will take place this spring in Paris.

Approximately 1,022 Student Members participate in local Student Chapter activities, as well as national conferences, poster competitions, student leadership forums, and the ISPE Annual Meeting.

By participating in a Student Chapter, students have access to networking opportunities, mentors (who can become their future employers), industry facility tours, professional development, interviewing practice, and other benefits that traditionally would not be so readily available.

Students, as undergrads, only get what is available to them by way of education, co-ops and internships, but the paths to working in the pharmaceutical industry aren't easily seen, according to Manfredi, who teaches in the pharmaceutical engineering Master's program at NJIT. "Most students, in the past, thought that with a degree in

chemical engineering, you could work in the petroleum and drug industries," he said. "There was no differentiation. ISPE opened the eyes for a lot of students to careers in health care."

"Joe, Jon and Jane Brown, and many other visionary ISPE Members who followed, had as their objectives to define pharmaceutical engineering, especially as it related to career opportunities, and to develop a joint program between industry and academia for job and technology development," said Connie Muia, retired ISPE Director of Chapters and Affiliates who helped expand the Student Chapter program.

"There are many former Student Members who are employed in the industry and serving in leadership roles at ISPE," she said.

Student Membership Fee: \$15 Shaping the Future of the Industry: Priceless

By the numbers, it's obvious that Student Members aren't exactly the most influential constituency in the Society or in the Industry. However, according to ISPE Members and staff, they will be very soon, and so they are too important to ignore.

"They are the future of ISPE and our industry," said Lynne Richards, ISPE Director of Affiliate and Chapter Relations. "The return on investment is demonstrated in the multitude of success stories from past Student Members who credit ISPE for its role in opening doors to unmatched opportunities that helped define the professionals they are today."

"I became involved because I wanted to provide students with opportunities to make career-choice decisions that weren't available when I was in college," said Brown. "As I worked with the students and helped them maintain their Student Chapters, I always came away feeling energized and excited because of their eagerness to learn about our industry and because of their positive attitudes."


"I also realized how much I learned from them each time I went to a Student Chapter meeting. It was a great way to give something back to the Society and made me feel like I was helping contribute to successful futures for the students."

Room to Grow

On average, ISPE establishes about one to two Student Chapters a year, and in the last year, chapter formations increased 10 percent, according to Paul Lammers, Chairman, and Bo Crouse-Feuerhelm, Past Chairman of the ISPE Student Development Committee (SDC).

Together with the University Relations Committee (URC), ISPE is looking at the possibility of implementing more initiatives with elementary and high schools and developing an international internship program, as well as a global student leadership institute.

Thanks to a handful of committed ISPE volunteers in the early '90s, the Student Chapter program is a worldwide success. The Society is seeking more committed volunteers to continue carrying the torch.

"I think what we do is very rewarding, and entertaining, both personally and professionally," said Lammers. "But we don't have enough Members in our committee. We're looking for people who have a passion for students and have time to commit." 

Special thanks to Connie Muia for her contribution to this article.

For more information on how to help shape the next generation of industry professionals by joining the SDC, visit www.ispe.org/getinvolved.

If you're a current or prospective Student Member and would like more information on what your future could look like in the industry with ISPE, visit www.ispe.org/campusconnection.

Dave DiProspero Honored with Max Seales Yonker Member of the Year Award

Dave DiProspero was awarded the Max Seales Yonker Member of the Year Award at the 2006 ISPE Annual Meeting. This prestigious award honors the ISPE Member who has made the most significant contribution to the Society during the past year.

DiProspero has been an ISPE Member since 1994 and has been heavily involved in all aspects of ISPE's educational development for several years, most recently as the Chair of the newly formed Training Advisory Committee. This past year he guided the initiative of the Certification Training Task Team to perform a gap analysis of programs available in the ISPE library compared to the competencies required within ISPE's new Professional Certification.

In this interview, he reviews his career, what is important in life, and his years volunteering with ISPE.

How did you come to join ISPE?

I joined ISPE in 1994 based on the recommendation of a good friend of mine, already involved in the Society. I had been working in the pharmaceutical industry for some time and knew of ISPE but was never a Member. I was told that ISPE was a great place to expand your knowledge, through the various educational offerings, as well as the place to network and meet others in the industry. With this in mind I signed up and took my first training course. I was quite satisfied.

Over the next few years I attended various meetings, events, and educational programs, without too much additional involvement. In the late 1990s I was approached to be a speaker at one of the conference programs. Reluctantly, I accepted and was introduced to a few of the volunteer leaders. I found these to include some sharp and dynamic people. The



From left to right: Jane Brown, ISPE Chairman, Dave DiProspero, Gert Moelgaard, ISPE Immediate Past Chairman.

session went very well and I was quite impressed with the inside working of the organization. This prompted me to reach out and see what other involvement options were available. I made contact with Bob Chew who found a place for me on the North American Education Committee, where I served for a couple of years. It wasn't long after that I got even more involved with ISPE, via authoring technical articles and becoming a conference leader for the Oral Solid Dosage (OSD) Tampa session. ISPE then gave me an opportunity to Chair an educational committee and become part of the International Executive Education committee. I've been involved at this level for several years now and am honored to be part of such an outstanding Society and dedicated group of individuals.

What is your title and what does your job entail?

I am a Principal in Stantec's Bio/Pharmaceuticals Group, Stantec Consulting Group, since 1993. Prior employers have included IEDCO, Glatt Air Techniques, Matcon USA, Teledyne, and Lightnin Mixer. Stantec Consulting Group is a large full-service architectural and engineering firm, serving a wide range of industries, including life sciences, which is my particular area of responsibility. I am a senior leader within the bio/pharmaceutical practice area and am typically involved in general consultation, front-end planning, strategizing and project set-up/implementation for our clients. This includes big pharma, generics, contract manufacturers, biotechs, and other firms.

My specific area of expertise is in Oral Solid Dosage Forms including the various aspects of OSD process, equipment, and facility layout. Additionally, I have business development responsibilities and work closely with our various regional leaders to help grow the pharma side of our business. Over the past couple of years, a rather large focus of my efforts has been in Puerto Rico where Stantec has built a strong local presence. Most recently I have been involved in developing and growing the business in the US Mid-Atlantic and Southeast, as well as the West Coast, where Stantec has multiple offices and strong engineering expertise. I am working for a great firm that has talented people, strong executive management, a solid growth plan and is well-positioned for further growth and longevity. Additionally, they fully support my volunteer work with ISPE.

Where did you receive your education?

I completed my undergraduate studies at the Rochester Institute of Technology in upstate New York. As a part-time evening student, I studied for about nine years in an interdisciplinary program and achieved a BS in business and electro-mechanical engineering. Over the course of my career I have attended a wide range of continuing education sessions in process, engineering and business.

Continued on page 4.



Dave DiProspero

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“Collectively, all of us are making a difference in this world and our efforts are helping people live longer, healthier, and happier lives.”

Dave DiProspero

How has ISPE helped your career?

ISPE has helped my career in several ways. As a pharmaceutical consulting engineer, it is of vital importance that I (and my firm) bring expertise and current knowledge on trends, technologies, regulations, and guidelines to our clients. The Society offers numerous avenues for staying current on these issues relating to our industry and I have taken advantage of these. Additionally, getting to know my peers in the industry, through membership and various events has allowed me to personally know who to turn to for advice and input on a given expertise. As a result, I have had reasonable success in my career and can credit ISPE for a good part of it.

What has been your best experience with ISPE?

Probably my best experiences with ISPE have been related to the people I have met and the friends I have made. The industry we work in is really a rather small community based around relationships. People frequently move from firm to firm or from one side of the industry to the other. ISPE allows you to stay in touch and make use of a great network, watching each other move on and advance in career. Via volunteering, I have gotten to meet some great folks and have been able to develop both personal and business relationships.

How did you feel when they announced your name as the winner at the ISPE Annual Meeting?

(President/CEO) Bob Best really caught me off guard on this one. I had no idea it was coming. That particular day I had a red shirt on and was later told that my face turned about as red as the shirt when my name was announced. Ironically, when I first saw Bob in Orlando, a few days before the Membership luncheon, he said to me that this was going to be my best Annual Meeting. I just smiled and said, I hope so, without any idea of what was coming.

As he started to talk about the 2006 Member of the Year, during the award presentation and the various committees this person served on and then elements of the work done by my Certification Training Task Team, I started to put the pieces together and thought, “No way, not me.” Then bang, my picture shows up on the big screen and my name is announced. Wow! It was a great feeling. It was excellent to be recognized for the value of my volunteer contribution and equally important to the support my company Stantec gives, allowing me to volunteer.

Do you know any of the previous award winners?

I actually know several of the previous award winners, all of whom I’ve met through ISPE. Last year’s winner, Randy Perez of Novartis, and I have served together on the International Executive Education Committee. I also know past winners John Nichols, Gordon Farquharson, Jon Tomson, Jerry Roth, and Jim O’Brien.

After spending some time with Jon Tomson at this year’s Annual Meeting, we learned that both of us grew up and spent a good part of our lives in Rochester, New York. We had a wonderful discussion about the city of Rochester and the various places we’d each go and things we used to do. As strangely as things work out, Jon and I currently live about 50 miles apart from each other, here in New Jersey.

I would have to say that I am now in pretty good company.

Did you know Max Seales Yonker (for whom the Award is named)?

Unfortunately I did not know Max personally. However, I was at the 2005 Annual Meeting Members Luncheon, when her husband Tom gave an emotional and moving talk about her life and struggle with her disease. I think everyone in attendance that day became a friend of Max and got to know her.

Tom’s talk also put a great perspective on the industry we work in and the contribution all of us make to the betterment of human life. Tom’s recognition of the many pharmaceutical companies and their products that helped extend Max’s life was enlightening. We often forget that when we are dealing with our day to day efforts of providing a service or engineering a system or getting wrapped in the details of a company operation or process. The Members of ISPE are working in an industry that brings great benefit to many.

What is your greatest accomplishment?

That is a very tough question. Hopefully the right answer is that I have not yet made my greatest accomplishment. It is still to come. However, one that does come to mind, which I consider significant, is maintaining a good balance between work and family. This seems to be difficult these days. Too often it ends up being one or the other. Rarely both. My wife and I have raised two kids who have a good head on their shoulders, a generally positive attitude, and a promising future ahead of them. We’ve successfully maintained strong family ties, all while building a career and dealing with relocations, business travel and other typical job-related issues. All in all I can say that I have done pretty well in family and career.

What are your hobbies?

Since a young age, music has always been and currently is a very big part of my life and is my major hobby and passion. I am actually the lead singer and acoustic guitar player for a Philadelphia-based classic rock cover band by the name of

Concludes on page 6.

ISPE Annual Meeting Leads Call for Change in Pharmaceutical Industry

The 2006 ISPE Annual Meeting was held 5-8 November in Orlando, Florida and its effects will be felt for years, as Members continue to work with industry leaders, regulatory agencies, and academia to lead the Society into innovative changes.

More than 2,000 ISPE Members and non-Members attended the meeting, the Society's premier opportunity and one of the industry's foremost occasions to bring pharmaceutical professionals together for interactive workshops, discussion forums, classroom seminars, and keynote sessions to explore major trends.

"Change" was a recurrent theme throughout the keynote speeches, and woven into more than 31 educational sessions were topics focusing on ASTM, Quality by Design, RFID trends, biotechnology, drug shortages, risk management, and more, representing more than 250 speakers over the successful four-day event.

Newly-elected Chairman of the Board, Jane R. Brown, addressed the changes by talking about the future including new ideas and new ways of working. "There will be challenges in the development of these new medicines, but many of the hurdles we now face will no longer exist because of the collaborations we are forming today between industry, regulatory agencies, and academia."

Brown, manager of GMP Compliance for GlaxoSmithKline, was officially named Chairman at the meeting and, along with her fellow Board members, attended the Annual Meeting to meet delegates, participate in committee and educational offerings, and help provide guidance for the industry's future.

The 2006-07 International Board of Directors include Vice Chair Bruce Davis, Treasurer Charles P. Hoiberg, Secretary Alan MacNeice, and newly elected Directors Joan Gore, Tomiyasu Hirachi, and John Nichols. Returning Directors include Gert Moelgaard (immediate Past Chair), Bob Chew, Jan Gustafsson, Linda McBride, Randy Perez, Andre Walker, Stephanie Wilkins, and Chris Wood.

Keynote Messages

Changes in the industry were outlined by keynote speaker Moheb Nasr, Director, ONDQA, CDER, of the US Food and Drug Administration (FDA), who gave the FDA's perspective on the need for strategic innovation in the industry. Nat Ricciardi, President of Pfizer Global Manufacturing (PGM), provided a snapshot of the challenges facing the industry today and discussed how innovation will lead the way toward successful adaptation to our new environment.

According to Ricciardi, some major industry challenges/pressures include new products; slower to market and ramp up; hostile external environment (media and public perceptions); decline of 'trust' in the industry; increased call for

generics; significant focus on cost (outsourcing); and government interventions.

How can we innovate? According to Ricciardi:

- always seek sustained value
- learn and apply best practices from non-pharmaceutical industries
- apply technology to mitigate external pressures on industry
- retain advantages of existing operating structures
- foster a culture of innovation all across
- bring effectiveness, stability, and predictability to a process before seeking efficiency

In addition, Moheb Nasr gave insight into the challenges facing the FDA. They include:

- public concerns and political pressures
- tight resources
- adequacy of expertise for a rapidly changing science and technology
- inconsistency of regional and global regulatory systems outside the US
- Quality by Design, product/process design and development, a robust quality system, and science- and risk-based approaches will help achieve the desired state of pharmaceutical manufacturing

Ron Branning, Vice President of Commercial Quality at Genentech, also delivered a keynote presentation concerning ISPE's new strategic plan and outlined challenges the pharmaceutical industry is facing. Some of those identified challenges include:

- generics are capturing a major share
- small molecule focus being replaced by large molecules
- lean manufacturing; shift to personalized medicine changing
- manufacturing process and new technology
- days of frequent blockbuster drugs are over
- cost of drugs; pressures from consumers
- R&D productivity declining
- patent exclusivity diminishing

The positive news? ISPE is looking at those threats and challenges and facing them head on.

"ISPE will embrace the future and is committed to playing an integral part of that future," said Branning. "That means planning and leading and collaborating with key industry professionals and regulatory agencies."

In addition to the education sessions and committee meetings, both ISPE and regulatory leaders were able to meet

Concludes on page 6.



Dave DiProspero

Continued from page 4.

Right Turn at 40. There are five of us, all professionals with successful careers by day. We do our best to get together and play by nights or weekends, as much as family and job responsibilities allow. For me it is a perfect outlet from the stresses of work and life and is great fun. We are keeping alive the classics from Lynyrd Skynyrd, Allman Brothers, Creedence Clearwater Revival, Eagles, Doors, ZZ Top, The Who, Eric Clapton, Bob Seger, and many others. Music the way it used to be. Beyond that, I like to travel and spend time with family and friends, enjoying life.


Who is in your family?

I have a great supportive family that is clearly the most important thing to me. I have to give them a lot of credit for putting up with me over the years. My wife Peggy and I have been married for 20 years and together for nearly 27. Wow!! Amanda, my daughter, will be 19 and is completing her first year of college, working toward a future in the health care industry, likely in nursing or maybe even the pharmaceutical industry. Who knows? My son David, 14, is a freshman in high school and an avid athlete, something he certainly doesn't get from me. Soccer, basketball, baseball, football, and whatever else he can play. He keeps us running year-round. In addition to my immediate family, we have many other family members and close friends with whom we try to spend as much time as possible.

Any other pertinent information that you feel Members would like to know.

I work very hard and often times go out of my way to maintain an upbeat and positive attitude on life. If the washing machine breaks, why get upset about it? Just go out and buy a new one. My boss at Stantec has given me the tag, "the glass half-full guy." I'm fine with this tag and prefer to live life this way, than any other. I try not to sweat the small things and put my focus and energies on the good, not the bad. My general feeling is that "life is great" and we all need to recognize that, use it to our benefit and enjoy. Whenever the end comes, I hope to have no regrets. Smile and laugh as much as you can, be nice to everybody and try to make a positive contribution to Society. Isn't that what it is all about?

I am very honored to have been chosen as the 2006 ISPE Max Seales Yonker Member of the Year. I would like to thank the Members, staff, and leadership for this recognition. I am proud to be an ISPE Member and volunteer and look forward to continuing contributions to the Society and great pharmaceutical industry we all work in. Collectively, all of us are making a difference in this world and our efforts are helping people live longer, healthier, and happier lives. It is the tragic diseases, such as the one that cut Max's life short, that should be our drivers in the daily work we are doing.

Thanks to all my friends in the industry. 

ISPE Annual Meeting...

Continued from page 5.

about critical issues, such as ICH Guidelines. They agreed to meet again in June during the ISPE Washington Conference in Arlington, Virginia, USA. ISPE Members can download video of the keynote session at www.ispe.org.

How ISPE will Help Lead the Change

In the new Strategic Plan, ISPE is firmly moving ahead as an "agent of change," offering concrete solutions, including plans to:

- promote industry innovation
- work and collaborate with regulators, industry, suppliers, and academia
- work with a global mindset but with local actions
- expand Membership into Process and Pharmaceutical Development
- play a major role in the pharmaceutical manufacturer of the future
- make a "stepwise" implementation
- proceed with innovation
- create a technology infrastructure to facilitate understanding and technological innovation
- provide forums for industry, suppliers, academia, and regulator collaboration

ISPE will continue to strive to lead the industry with the newest and most necessary education courses, Webinars, technical documents, and scientific journals to provide education and professional development for its Members.


Be sure to visit www.ispe.org to view photos of award winners and Annual Meeting attendees, and learn more about the events of the 2006 Annual Meeting. Next year, the Annual Meeting will be held at Caesar's Palace in Las Vegas, Nevada.

See You in Las Vegas for Next Year's Annual Meeting

After the great success of the 2006 annual meeting, be sure to sign up for next year and make sure it's in your budget.

We have received an overwhelmingly positive response during and after the meeting. The meeting included up to the minute educational sessions, information on our new CPIP certification, our new *Journal of Pharmaceutical Innovation*, and more than 280 vendors in the exhibition hall.

Your next chance will be 4-7 November 2007 at Caesar's Palace in Las Vegas. Join pharmaceutical innovators from around the world for the premier opportunity of the year to network with an international roster of industry professionals. It features a host of important sessions, with a special seminar reviewing the Baseline Guide for Oral Solid Dosages - new for 2007.

Watch www.ISPE.org for complete details and on-line registration. Event includes networking receptions, table top exhibits, and sponsorship opportunities. To register, please call customer service at +1-813-960-2105. 

April Paris Conference Highlights Nano and Micro Technology, and More

ISPE will hold its first European conference of 2007 in Paris, **16-19 April**, at the Hilton Hotel. One of the highlights will be the Nano and Micro Technology poster presentation (see article on page 90) showing innovative concepts from the industry's and academia's finest minds.

The ISPE Paris Conference program will include eight seminars presented by industry leaders on the following key topics:

16 APRIL

Revision of the *GAMP*® Good Practice Guide: Validation of Process Control Systems

Seminar Leaders: Mark Cherry, AstraZeneca, UK; Martin Isherwood, Eli Lilly, UK

Since the *GAMP Good Practice Guide: Validation of Process Control Systems* was first published, there have been developments in a number of areas – risk assessment and Process Analytical Technology (PAT) being two specific examples. This seminar will discuss the revisions to the Guide which take into account of such changes and, additionally, expand the consideration of global regulatory requirements. The revisions will also provide a clear understanding of the roles of the end users and suppliers, including suppliers of base applications and systems integrators.

The seminar will be based on work carried out by the Process Control Systems Special Interest Group (SIG) of the GAMP Forum to improve understanding of current regulatory trends governing the use of automated systems in the pharmaceutical industry.

16-17 APRIL

Nano and Micro Technology for Pharmaceutical Products and Processes

Seminar Leaders: Chris Dowle, The Centre for Process Innovation (cpi), UK; John Nichols, Foster Wheeler, UK; Tom Taylor, The Centre for Process Innovation (cpi), UK

Technologists using the fundamental characteristics of nano and micro technologies are currently providing solutions to applications across a broad spectrum of industries; this is a rapidly developing area. This seminar gives an up-to-date understanding of the underlying science; industrial manufacturing technologies; the range of product applications; and environmental, safety, health and quality impacts. It includes nano particle generation, use of microreactors and nano diagnostics.

Process Analytical Technology (PAT)

Seminar Leaders: Ian P. Flawn, Ferring Pharmaceutical A/S, Denmark; David Selby, Selby Hope International Ltd., UK

PAT is a buzzword within the industry and yet it still holds many mysteries for us in everyday terms. There is no doubt that PAT is pivotal to any company achieving manufacturing excellence, it has an ongoing impact on Quality Systems and modifies key activities such as process development and the management of data. This seminar will look at the key aspects of PAT and how effective process control benefits manufacturing. First-class speakers will explain how the improved understanding of the process can lead to increased yields and reduced waste, shortened cycle times and ultimately delivers improvements in product consistency at reduced cost.

Pharmaceutical Water, Regulation and Innovation

Seminar Leaders: Robert Walker, Robert Walker GMP Consultancy Ltd., UK

Pharmaceutical water systems are critical in virtually every aspect of API and dosage form manufacture and regulators will subject them to scrutiny. This seminar will provide cutting-edge information about ISPE's new Good Practice Guide and use case studies and experts to highlight developments,

technology and materials to help provide flexible and effective systems.

17 APRIL 2007

Facility of the Year Exposé

Seminar Leaders: Tony Felicia, AstraZeneca, USA; Andrew Signore, Integrated Project Services, USA

The ISPE Facility of the Year competition has been running for the last three years and receives dozens of entries each year from major and emerging pharmaceutical companies. In the past the award was won by Novo Nordisk (2005) and Baxter (2006).

ISPE, INTERPHEX, and Pharmaceutical Processing magazine spent 2006 looking for the facility project that demonstrates global leadership; one that showcases cutting-edge engineering, innovative new technology or advanced applications of existing technology.

This awards program is about much more than just the science and technology of the facilities. It is about recognizing the shared commitment and dedication of individuals working for different companies worldwide to innovate and advance pharmaceutical manufacturing technology for the benefit of all global consumers.

18-19 APRIL

Biosafety

Seminar Leaders: James V. Blackwell, BioProcess Technology Consultants Inc., USA; David Harrison, Amgen, USA

This seminar will clarify the different design requirements for each biosafety level. Speakers will highlight the various regulatory requirements associated with each level and describe which elements define the appropriate biosafety level for deployment. Delegates will have an opportunity to hear about case studies on design, validation and implementation of systems complying with the different biosafety levels.

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April Paris Conference...

Continued from page 7.

Design Space

Seminar Leaders: Jan Gustafsson, Novo Nordisk A/S, Denmark; Pierre le Meur, SPEC Conseils, France

Introduced with ICH Q8, the new concept of Design Space is defined in the ICH Q8 guideline glossary:

“Design space is the multidimensional combination and interaction of input variables (e.g. materials attributes) and process parameters that have been demonstrated to provide assurance of quality. Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval.”

In this interactive discussion seminar speakers will explain the details behind this definition. Delegates will explore the reality of Design Space in today's pharmaceutical industry and will examine what should be provided under this concept in the application file and during a regulatory inspection, as well as during any audit.

Seminar speakers will explain both a no change and a regulatory change scenario and they will point out the challenges in the post-approval process.

Industry and regulators will elaborate on how design space can be implemented into daily practice within different aspects of the pharmaceutical industry (sterile production, biotechnology, APIs, etc.).

Project Management - Facing Today's Challenges

Seminar Leaders: Andrew Ingleby, AstraZeneca, UK; Trish Melton, MIME Solutions Ltd., UK

Professional project management is a requirement in all industries, but presents particular challenges in the pharmaceutical industry. So often many projects are poorly managed and do not deliver their business success criteria.

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Nano and Micro Technology Posters Wanted for Presentations

The ISPE Paris Conference will see the launch of the Nano and Micro Technology poster presentation from the industry's and academia's finest minds. Poster presentations will be on display from **16-17 April 2007** at the Nano and Micro Technology Seminar.

Topic Categories

- Use of Microreactors for Pharmaceutical Processes
- Nanotechnology in Pharmaceutical Products
- Nanodiagnostics
- Relevant Metrology

Benefits of Presenting a Poster

- Exposure to 500 pharmaceutical industry professionals at the ISPE Paris Conference
- Abstracts will be displayed at the ISPE Paris Conference
- Forum for presenting work, communication topics, trends and ideas
- Less formal, interactive environment

Eligibility

- Professionals from the pharmaceutical, biotechnology or medical device industry
- University/college faculty
- Students

Timelines

Deadline for Submissions:
26 February 2007

Presenter Notification Date:
12 March 2007

Rules and Guidelines

- Presenters will develop panel sections for the project abstracts, background information, materials and methods, graphics and charts if suitable.
- Abstracts must demonstrate sound technical content.
- Abstracts must not exceed 400 words.
- Number of submissions allowed per person: 3
- The size of the posters should be approximately 1 m × 1.5 m. Posters

will be displayed vertically.

- Posters must be fully-assembled and ready for viewing by 09.00 on Monday, 16 April 2007.
- No commercial advertisements are permitted. One discrete company logo is permitted.
- Collaborative poster presentations are acceptable. All researchers must be acknowledged on the poster.

Submission

To submit an abstract, please complete the submission form available at the website www.ispe.org/parisconference and submit it by e-mail to nanoposters@ispe.org. Early submission of an abstract is encouraged.

Review Criteria

Submissions will be reviewed by the Nano and Micro Technology seminar leaders and ISPE Education Advisors for technical relevance, merit and organization. Those deemed most appropriate/innovative will be chosen for display at the ISPE Nano and Micro Technology Seminar.

Poster Presentation Schedule

- Poster Presentation Set Up
Sunday, 15 April, 17.00 - 19.00
- Monday, 16 April, 08.00 - 09.00
- Poster Presentations on Display
Monday, 16 April
Tuesday, 17 April
- Poster Presentation Break Down
Tuesday, 17 April, 17.00 - 18.00

Contact

Any questions about the poster presentation?

Please contact the Nano and Micro Technology seminar leaders:

John Nichols, Foster Wheeler, UK
E-mail: John_Nichols@fwuk.fwc.com

Chris Dowle, The Centre for Process Innovation (cpi), UK
E-mail: chris.dowle@uk-cpi.com

Tom Taylor, The Centre for Process Innovation (cpi), UK
E-mail: tom.taylor@uk-cpi.com




April Paris Conference...

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This seminar will provide delegates with examples of some of the key challenges faced within pharmaceutical projects and the tools to deliver the obligatory quality, time, cost and regulatory compliance requirements of any project.

This seminar will focus on the benefits of well-structured and controlled pharmaceutical projects as highlighted by real life experience and case studies and is supported by the Project Management Community of Practice (PM COP).

For more information and to register, please go to www.ispe.org/ParisConference. 

Tampa Conference 2007 Scheduled for February


Seminars on **Aseptic Processing**, the new ISPE Packaging, Labeling and Warehousing Operations (PACLAW 2007) Baseline Guide, **Oral Solid Dosages**, **Sterile Manufacturing Facilities**, and much more are scheduled for the ISPE Tampa Conference, 12-15 February 2007, Hyatt Regency Tampa, Tampa, Florida, USA. For details and to register, visit www.ispe.org/tampaconference.

Sponsorship and table top exhibition opportunities are available for the ISPE Tampa Conference. For details, please contact Dave Hall, ISPE Director of Sales, by tel: +1-813-960-2105, Ext. 208, or e-mail: dhall@ispe.org. 

Find Solutions to Daily Work Problems at the ISPE Copenhagen Classroom Training

Get the edge you need to succeed and register for the ISPE Copenhagen Classroom Training, **26 February - 1 March 2007**, Copenhagen, Denmark. This course covers topics such as computer systems validation; biopharmaceutical process development; pharmaceutical water systems; risk management; GMPs; and application of commissioning and qualification.


ISPE Classroom Training offers you a variety of courses to meet your needs for skills and practical knowledge and is a recognized opportunity for in-depth, topic-specific learning. Take this opportunity in order to enhance your career development and to find valuable solutions to daily work problems.

For more information and to register please visit www.ispe.org/CopenhagenTraining. 

Mark Your Calendar with these ISPE Events

March 2007

- 1 San Francisco/Bay Area Chapter, Vendor Night, South San Francisco Conference Center, South San Francisco, California, USA
- 8 San Diego Chapter, Extended Education Class, La Jolla, California, USA
- 14 Great Lakes Chapter, Spring Meeting, Merrillville, Indiana, USA
- 15 Greater Los Angeles Area Chapter, Technical Training, California, USA
- 19 - 22 2007 San Francisco Classroom Training, The Fairmont, San Francisco, California, USA**
- 21 Carolina-South Atlantic Chapter, 2007 Annual Technology Show - Quest for the Best!, Exhibits, Education Seminars, and Keynote Speaker, Durham, North Carolina, USA

Dates and Topics are subject to change 

Architects, Engineers - Constructors

CRB Consulting Engineers, 7410 N.W. Tiffany Springs Pkwy., Suite 100, Kansas City, MO 64153. (816) 880-9800. See our ad in this issue.

IPS - Integrated Project Services, 2001 Joshua Rd., Lafayette Hill, PA 19444. (610) 828-4090. See our ad in this issue.

Parsons, 150 Federal St., Boston, MA 02110. (617)-946-9400. See our ad in this issue.

Bioreactors/Fermenters



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AES Clean Technology, 422 Stump Rd., Montgomeryville, PA 18936. (215) 393-6810. See our ad in this issue.

Employment Search Firms

Jim Crumpley & Associates, 1200 E. Woodhurst Dr., Bldg. B-400, Springfield, MO 65804. (417) 882-7555. See our ad in this issue.

Filtration Products

Siemens Water Technologies, 125 Rattlesnake Hill Rd., Andover, MA 01810. (978) 470-1179. See our ad in this issue.

Label Removal Equipment

Hurst Corp., Box 737, Devon, PA 19333. (610) 687-2404. See our ad in this issue.

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Active Chemical Corp., 4520 Old Lincoln Hwy., Oakford, PA 19053. (215) 676-1111. See our ad in this issue.

Astro Pak Corp., 3187 Redhill Ave., Suite 105, Costa Mesa, CA 92626. (800) 743-5444. See our ad in this issue.

Cal-Chem Corp., 2102 Merced Ave., South El Monte, CA 91733. (800) 444-6786. See our ad in this issue.

Oakley Specialized Services, Inc., 50 Hampton St., Metuchen, NJ 08840. (732) 549-8757. See our ad in this issue.

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ProPharma Group, 10975 Benson Dr., Suite 330, Overland Park, KS 66210; 5235 Westview Dr., Suite 100, Frederick, MD 21703. (888) 242-0559. See our ad in this issue.

Water Treatment

Christ Pharma & Life Science AG, Hauptstrasse 192, 4147 Aesch, Switzerland. +41 617558111. See our ad in this issue.

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