This article describes Site Master Planning in the context of corporate strategic planning. The various dimensions of physical planning are seen as means of advancing corporate goals. Moreover, the successful plan is one that integrates facilities, process, site design, and infrastructure in recognition of their interrelated impacts on achieving strategic goals.

Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Journal of ISPE
January/February, 2001 Vol. 21 No. 1

Integrated Strategic Planning: New Horizons for Infrastructure, Image, Function, and Business on the Pharmaceutical Campus

by Gary D. Anderson, PhD, and David M. Jonik, PE

Overview: The Relationship of the Business Plan, Master Planning and Site Operations

Master planning is a reflection of corporate vision. The success of any master plan is dependent upon a planner's ability to translate the business plan, as developed by corporate management, into a planning vision to guide future physical development. Physical development has many dimensions – from the purely functional to the purely aesthetic. A good plan uses all of these dimensions as tools to advance corporate goals. Therefore, master planning on pharmaceutical campuses needs to address facilities, plant processes, site layout and design, and infrastructure. Site design and architecture can enhance image; functional relationships – whether in facilities or process layout – can promote efficiencies of operation, and infrastructure planning can help to realize economies in the procurement of energy and utility services and in waste handling. To best utilize the site, and to derive optimal benefit from all of these components, each must be developed in conjunction with the others. By taking an integrative, strategic approach to all aspects of planning, the best results can be obtained.

What do we mean by *integrative*? Figure 1 shows an integrative approach in relating the overall planning process to the ultimate outcome of site design and operations. The left side of the diagram represents the various components of the planning process. The diagram begins on the left-hand side with the corporate *business plan*. The business plan sets the overall direction for the company and may address everything from corporate image to product range and marketing. It is one of the main determinants of requirements relative to processes and facilities. These requirements are identified and satisfied through *facility planning* and *process planning*, indicated by the two boxes to the right of the corporate business plan. In turn, the results of facilities planning and process planning help to determine infrastructure requirements, which are addressed through *infrastructure planning*, the next box to the right. (The infrastructure planning process is shown in more detail in Figure 2, and will be discussed further below.) Together, the three types of planning (process, facility, and infrastructure) are encompassed by Site Master Planning.

An important outcome of the overall site master planning process is the degree of success with which the *operation* of the site fulfills business plan objectives. Site operation is shown diagrammatically on the right side of the diagram (and is portrayed in more detail in Figure 3).

An *integrative* process recognizes that all three of the site planning activities – facility, process, and infrastructure – are interrelated. All contribute to fulfilling the objectives of the corporate business plan, and all affect the ultimate success of site operations. None possesses absolute primacy over the others. For this reason, they should be considered concurrently.

Many large pharmaceutical companies have established campuses that meet the needs of administration, research, and manufacturing through physical design and planning. Due both to the specialized nature of company products and processes, and the importance of the public's perception of the company, pharmaceutical companies must present a modern, well-organized and inviting image not only in their internal facilities, but also in their overall outward appearance. In other words, a successful facility must address aesthetic as well as functional issues.

Problems Associated with Evolution and Change

Sometimes, however, the past history of a pharmaceutical site makes this objective difficult to achieve. The configuration of a pharmaceutical company's campus is often the result of decades of sequential growth and adaptation to ever-changing commercial, technological, organizational, and regulatory environments. The result of this continual adaptation presents problems not only for master planning, but also for day-to-day technical issues which are driven by corporate policy, supply parameters, regulatory issues, and other factors.

Facilities and elements of utility systems that were not designed to serve the exact functions they are called on to perform today exist side-by-side with state-of-the-art elements, some of which depend on antiquated services for support. The configuration and spatial relationships among related or unrelated facilities and utilities are likely quite different than how they would be designed today to serve purpose-built facilities.

This situation is not unusual. It is the natural outcome for any successfully self-sustaining organization with a respect for the careful use of resources and a standing commitment to the community. On the other hand, this situation does make it more challenging to improve, campus-wide, the overall appearance of the campus, as well as the configuration of processes and the complex infrastructure that has evolved to support both facilities and processes.

Moreover, change never ends. Just as the evolution of current infrastructure often results from past needs for adapting to change, any renovated infrastructure also will likely be called upon to support a continually changing campus in the future.

Applying the Strategic Planning Process to Site Master Planning

What is the role of *strategic planning* in site master planning? One challenge is that – just as the evolution of current facilities and infrastructure on a campus may have resulted from a continual need to adapt to change – there is every reason to believe that renovated or new development will likewise be called upon to support a continually changing campus. To accommodate and support these changes, strategic planning provides an on-going *process*, in contrast to a "one-shot" development plan. Although the creation of development plans represents important events in the strategic process, any given development plan is likely to have a limited useful life span, simply because the context in which it was created is subject to change. Strategic planning continually monitors the factors that should have an impact on a successful plan, and makes adjustments when these factors change. What are these variable factors? They include the corporate business plan, which is itself strategic in nature. They include the state of technology, the cost of operations, and environmental legislation that defines acceptable levels of environmental impact. They include, especially in a deregulated economic environment, the cost of purchasing energy and utility services. In the case of image or aesthetics, they may even include fashion.

Figure 2 represents the Strategic Planning Process. This process could be applied to the overall site master planning process or to any aspect of it (process, facilities, circulation, utilities), but here it has been specially adapted to reflect infrastructure planning. Even as shown, it is applicable to virtually any utility or infrastructure system. By itself, the column of boxes in the center of the diagram represents a perfectly acceptable approach to developing a "one-shot" plan. Generally, the actions represented by the boxes proceed from (1) gaining an understanding of the thing to be planned and the external parameters that affect it, through (2) developing alternative planning and design responses, and (3) evaluating those alternatives relative to cost and other pre-established objectives (such as might be derived from the corporate business plan), culminating in (4) the selection and development of a preferred alternative.

There are several features, however, that distinguish this strategic planning process from the "one-shot" approach. Most of these features are represented by activities in boxes that diverge from the central column. First, near the lower third of the column are two activities that interact: *Develop Alternative Design Responses* and *Develop Alternative Operating and Management Responses*. This reflects the recognition that planning is more than merely the manipulation of physical features. Strategic master planning recognizes that there is interplay between operations and design and that there are often possibilities to adjust both sides of the equation. For example, a change in the way a function is performed may obviate the need for a physical planning or design change. If adjusting the function is not detrimental to its operation or outcome, this can mean a savings in cost achieved by foregoing new construction or renovation. Strategic site master planning should not accept current procedures as givens.

Another feature that distinguishes strategic planning is illustrated in the diagram by several of the activities that are shown to the left of the central activity column. In general, these collateral activities represent a recognition of the impacts of factors that are completely exogenous to the system being planned. In some cases, these factors are even located off-site and may include market conditions or environmental exigencies as noted above.

Yet another characteristic that distinguishes the strategic approach from the one-shot approach is demonstrated by the feedback loops which are shown in the diagram. These operate at various levels. As shown in the diagram, one such feedback loop demonstrates how the determination of costs can lead to a re-evaluation of alternatives. (The arrow from the *Cost* box goes against the general flow of the other activities and returns to the *Evaluate Alternatives* box above it.) In fact, this is only one of several such feedback loops that operate throughout any planning process: decisions are continually re-evaluated in light of new information that is developed as planning activities proceed.

Of utmost importance is a more macro-scale feedback loop that leads from the final activity box (*Select Alternative and Refine Recommendations*) back to near the top of the process (*Analyze System Operation*). This arrow represents the continual monitoring of parameters as mentioned above. If the system or the external parameters that affect it have not changed, revisiting the process should not yield any new planning needs. On the other hand, a change that occurs anywhere along the process *may* indicate the need for planning action, depending on how that change is interpreted and acted upon in the numerous evaluation steps. Instituting an iterative approach, such as this, helps to ensure that site design and operation are fine-tuned to the environmental, cultural, and business contexts in which they exist.

As mentioned above, this strategic process can apply to *any* aspect of site master planning. Take planning for image and

aesthetics: Is post-modern architecture "out" and deconstructionist "in"? Maybe it's time to re-evaluate your image relative to the cost of updating it – taking into account, of course, exogenous system elements such as the State Historic Preservation Officer (SHPO) and the design guidelines in affect within the local planning jurisdiction.

Special Problems and Solutions Related to Infrastructure Planning: Planning-Level Modeling

Infrastructure represents a special challenge in the context strategic planning. That is the nearly unmanageable degree of detail required to examine each special case and to propose solutions to every shortcoming involving an energy system or infrastructure across an entire campus. Monitoring these complex systems is complicated enough, but what happens when changing parameters suggest a change in design or operation? Evaluating the effects of proposed adjustments and improvements not only on the system itself, but on all of the other systems addressed by site master planning, can border on the impossible, especially on large, multi-functional campuses. For campus-wide planning purposes, one means of dealing with this complexity is to limit the level of concern to the study of major elements of infrastructure systems - those lines that connect facilities or major lines that feed secondaries from on- or off-site sources. Even at this level, however, the number of elements and linkages and the ranges of operating parameters for all of the pertinent systems is daunting. For this reason, it is helpful to formulate models of the systems to evaluate how proposed improvements will affect their performance under different planning assumptions.

Figure 1 shows such a model in very broad outline under the *Plant Design and Operation* side of the diagram (the right-hand side). In this diagram, the *Infrastructure Planning* activity, from the left-hand, *Planning*, side of the diagram feeds directly into the rectangle of a similar color labeled *Infrastructure Design and Operation*, on the right-hand *Design and Operation* side. Below the Infrastructure *Design and Operation* box is a wide arrow pointing downward and labeled *On-Site Processes and Consumption*. The concept here is that site infrastructure supports on-site processes, whether they be manufacturing or other types of consumption (e.g. fuel consumed in heating or cooling an administration building). Superimposed over these two systems is an arrow labeled *Essential Services*. *Essential Services* is in fact a component of the overall bundle of infrastructure systems, but it carries out the specialized function of controlling and orchestrating the other infrastructure systems, even to the point – in well planned and engineered sites – of controlling

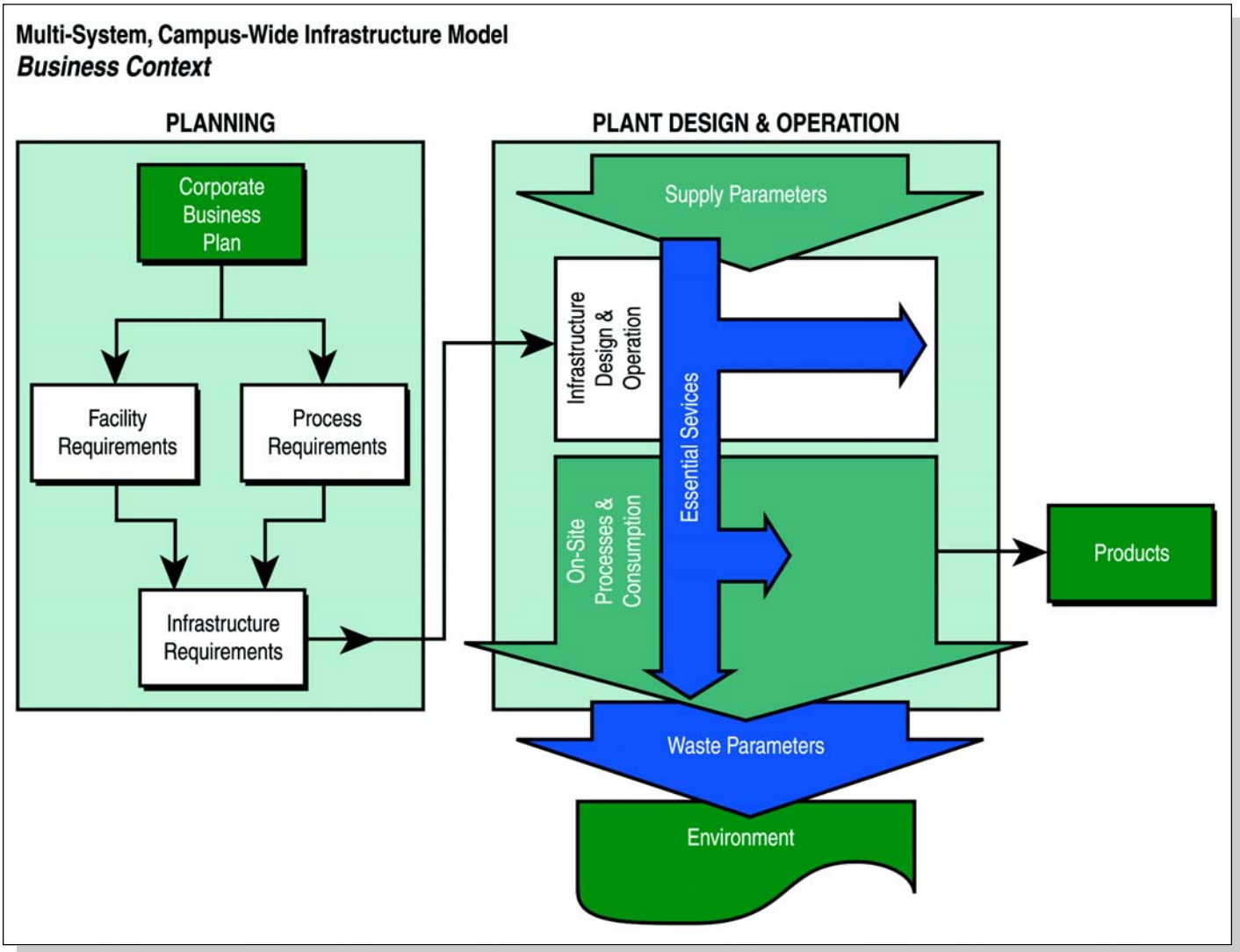

Figure 1. Multi-system, campus-wide infrastructure model - business context.

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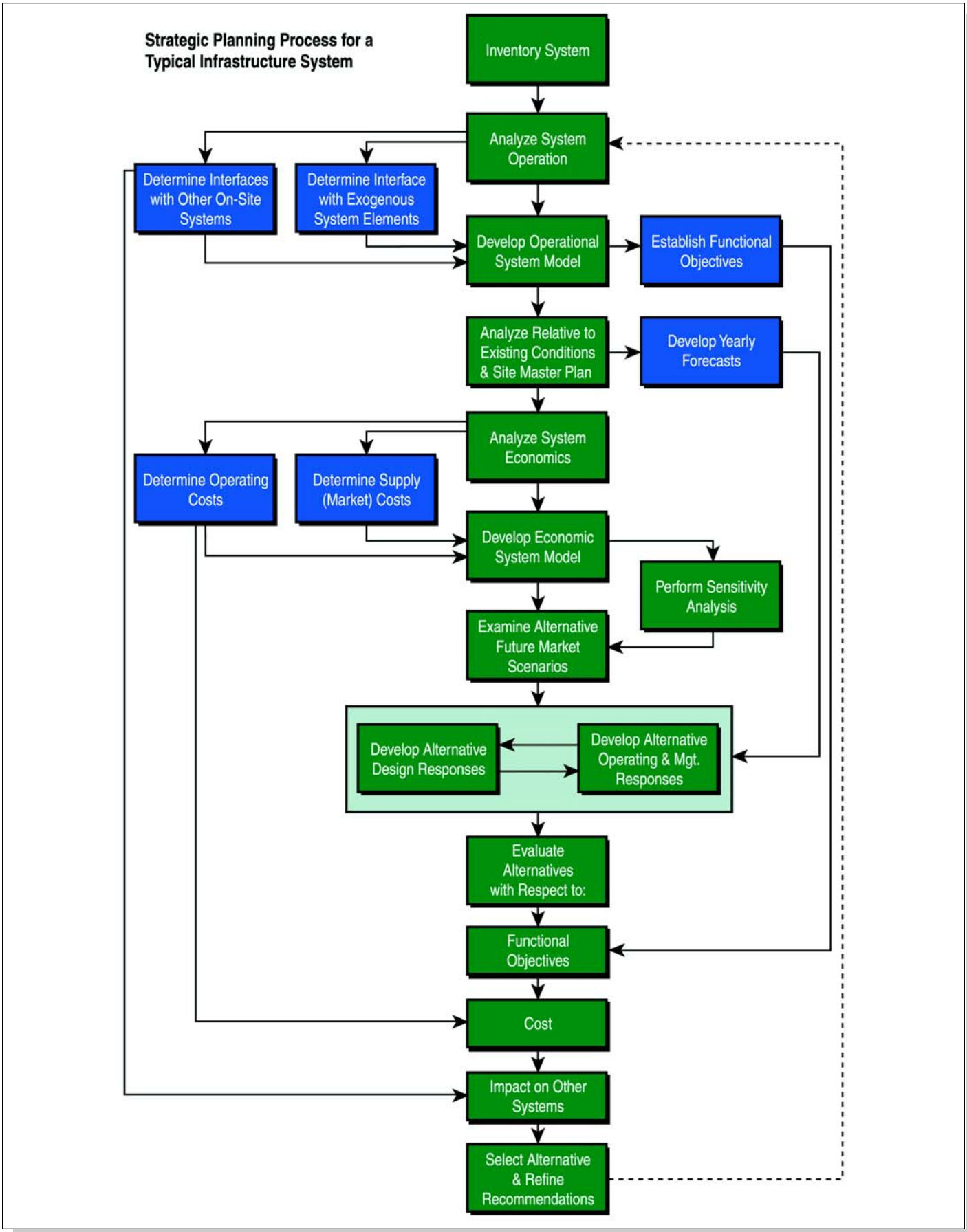

Figure 2. Strategic planning process for a typical infrastructure system.

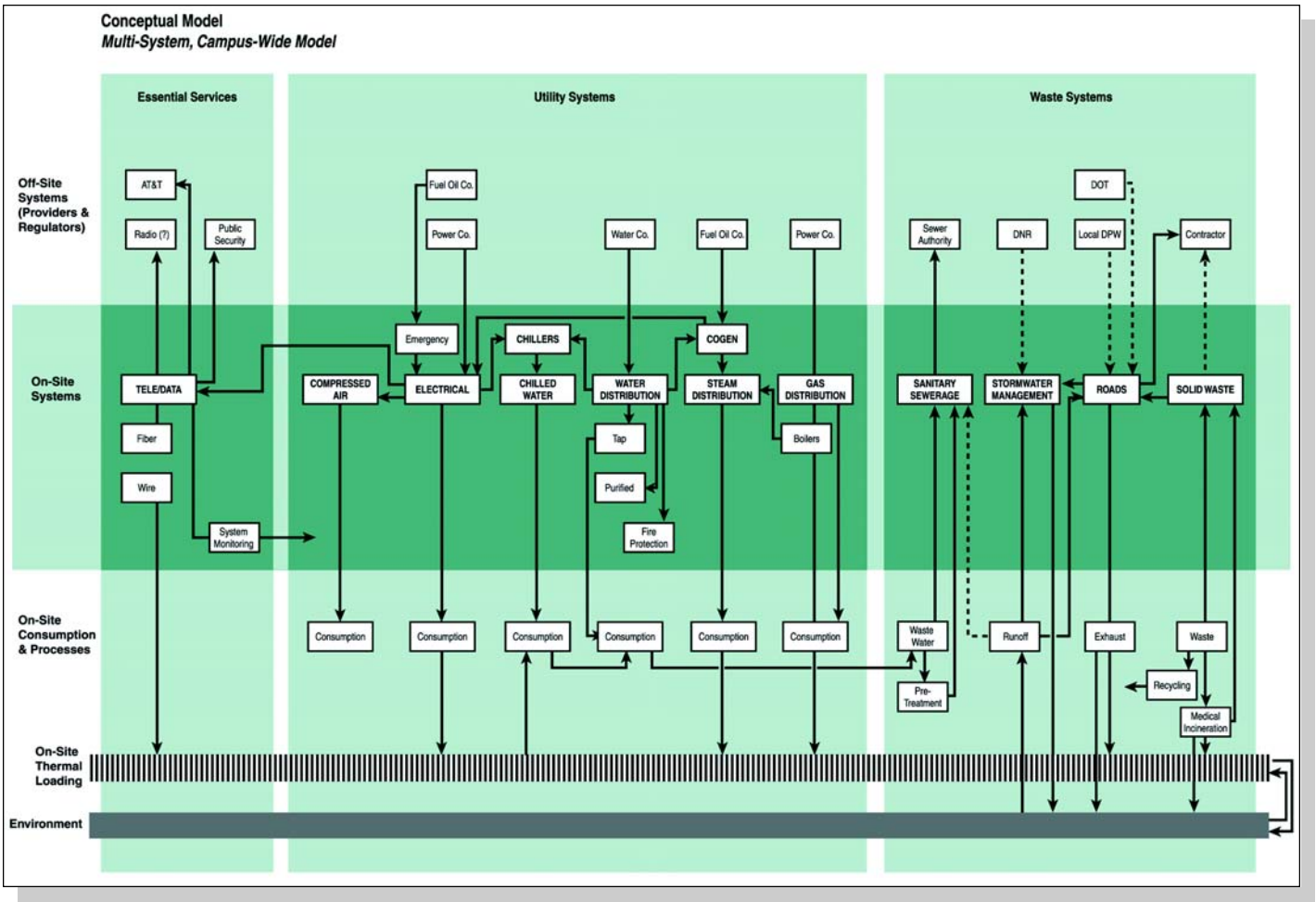

Figure 3. Conceptual model - multi-system, campus-wide model.

some functions within processes and facilities.

Feeding into these three on-site components (Infrastructure, Processes, and Essential Services) are *Supply Parameters*, indicated by the broad arrow at the top of the column. Supply Parameters comprise the cost and availability of energy and utility services, as well as the actual operation and configuration of off-site supply systems and the manner in which they interface physically with on-site systems. Flowing from *On-Site Processes and Consumption* are *Waste Parameters*, shown in the diagram by the broad arrow. Waste from on-site processes and consumption includes waste water, sewerage and run-off, solid waste, heat, noise, particulate matter, and numerous chemical discharges. Most waste eventually returns to the *Environment*. The *Essential Services* function (or arrow in the diagram), in addition to overlying and penetrating the *Operation* and *Consumption* functions, spans from the *Supply Parameters* to the *Waste Parameters*. It is this control system that can adjust day-to-day or minute-to-minute operations and can adjust to changing supply and waste requirements or opportunities in order to improve on-site efficiencies and economies relative to the all-encompassing, off-site macro-context. It can be seen from this simple diagram that Essential Services plays a critical role in maintaining the *sustainability* of the campus.

Figure 3 represents a conceptual model to describe in more detail, but still greatly simplified, the various systems that comprise an *Infrastructure Master Plan* for a pharmaceutical campus. The diagram is arranged along the same lines and reflects the same general relationships as those in the *Design and Operation* side of Figure 1. In Figure 3 *Off-Site Systems (Providers and Regulators)* are located at the top of the diagram and correspond to Supply Parameters in Figure 1. In a strategic planning process, these systems are continually monitored in order to adjust in a timely manner to changes that may represent opportunities or problems (e.g. changes in price structure due to deregulation). As in Figure 1, the lower portion of Figure 3 represents consumption, waste, and environment. In Figure 3, the central horizontal band represents the *On-Site Infrastructure Systems*. On pharmaceutical campuses, this is a technical area which can influence and be influenced by integrated strategic planning. The horizontal band cuts across three vertical columns which represent three main categories of infrastructure systems: *Essential Services*, *Utility Supply Systems,* and *Waste Removal Systems*.

In Figure 3, all of the infrastructure systems are shown concurrently. This simple model shows that many of the systems are interrelated even across the lines of the major categories. The implication is that external influences on one system may very likely have wide-reaching impacts on others as well.

Integrated strategic planning, as applied to site infrastructure planning, focuses on the white boxes in the diagram that appear on the band labeled *On-Site Systems*, as well as on the lines that connect the various activities, processes, and organizations represented by the other boxes above and below the

On-Site Systems band. What goes on inside the shaded boxes is usually not subject to planning recommendations developed through the process of campus master planning, and must be accepted largely as given, but variable. The contents of those will determine the parameters within which the on-site infrastructure systems must operate. These parts of the model, external to the systems themselves, can be treated as "black boxes." (Of course, recommendations concerning further study of these "black boxes" may be included in the master plan if it becomes clear that any of them has an impact on the infrastructure that might be improved with adjustments to internal operations.)

Summary: The Benefits of Integrated Strategic Master Planning for Pharmaceutical Campuses

How does a concern for integrated and strategic master planning affect what we normally think of as site master planning? An integrated strategic master plan will present the pharmaceutical company with opportunities derived from the macro-environment which can be capitalized upon with the assistance of operational models. These models may be formulated from detailed information, but are simplified in order to highlight important *relationships* rather than minute elemental descriptions. Using these approaches, the total master planning effort will address facilities, siting issues, interrelationships with the surrounding community, transportation, site material, vehicular and pedestrian circulation, and the solutions to many of the utility-related problems, some of which arise through the gradual evolution of the campus.

The result will be a site master plan that not only deals with aesthetics and basic functional layout, but which also can:

- improve operational efficiency
- ensure balanced development
- set the stage for further development
- capitalize on the changing macro-context rather than fall victim to it
- enhance sustainability
- advance the objectives of the corporate business plan

An Illustrative Example

STV Incorporated's master plan for a Belvidere, NJ, vitamin production facility provides a real-world example of the integrative strategic approach to pharmaceutical campus planning. Activities at the site included administration, research, production, and distribution. STV was asked to develop a conventional physical campus plan for the 500± acre site on the Delaware River.

However, before beginning to explore opportunities for the physical arrangement of facilities on the site, STV assessed the utility infrastructure at the macro level. Our appraisal of the interrelationships among power and steam generation, consumption, and the impact of deregulation led to the recognition that a new cogeneration plant might be brought on line. Also, our analysis of environmental regulations and required compliance at the plant led to recommendations for a different approach to stormwater management procedures, calling for limited containment and treatment of "first flush" stormwater. This ultimately saved capital funds that would otherwise have been required to increase the wastewater treatment facility, while still meeting strict environmental guidelines.

It was only after these basic functional issues were addressed that the more traditional components of campus master planning proceeded – with an analysis of functional relationships among activities, project growth in various organizational units, and attention to the image that management wished to address at the site. Melded into these considerations were significant new spatial determinants – the potential cogeneration plant and the land required for stormwater management – which would not have come to light without integrating considerations that fell outside the normal concern of a physical campus plan. The result was a physical development plan that was more sustainable in that it would be less vulnerable to major changes resulting from inevitable engineering developments.

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Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Journal of ISPE
January/February, 2001 Vol. 21 No. 1

Application of a Capability Study to a Syringe Filling Operation

Part 2 of 2: Protocol Execution, Data Collection, Analysis and Discussion

by Peter A. Hugunin

In Part 1 of this article, we discussed the utility of capability studies in factory acceptance testing, validation testing, and documentation to meet both production and regulatory requirements. We closed Part 1 with a prepared protocol. In Part 2, we execute the protocol, verify model validity, analyze the data, and report on the findings. In doing so, we illustrate how data are collected, transformed into information about the equipment or process, and this information itself into productive knowledge.

On-Site Adjustments

Prior to execution of the machine capability study all installation and most operational qualification attachments were executed. Hose type and identification was recorded; pump type and serial numbers were recorded; information on fill needles verified or taken; the machine and trays leveled; the operation of the machine checked, and the individual syringes weighed and tagged (see scatter diagram in Appendix 1 for information on syringe variability). In spite of these and other preparations, some field adjustments were necessary to make the testing more meaningful and successful. These changes, most naturally, resulted first from a discussion with the planned equipment operator (the day before departure); and next from the kick-off meeting with the OEM engineers and technicians just minutes before starting data collection. Three field modifications resulted:

First: The manufacturer's operator had identified *break time* as meaningful to the process, and although a process as opposed to a machine variable — it was a manual operation for the process under study — it was considered very important and useful information. Consequently, during execution we introduced a process variable: *Time between loading* of Tray (TL). We decided to vary this time between TL1 and TL2 to test what affect it might have on fill volume and to remove these samples from further statistical analysis as necessary.

Second: The OEM technicians and engineers informed us that we could not operate at top speed. *Speed* must be set at something other than maximum. Reportedly it could not be guaranteed that the fill needles would be fully retracted from the syringes before movement began. This might result in broken or bent fill needles. Also, a problem with vibration might result at top speed given the small fill volume we had selected for testing. Rather than risk both damaging the equipment and aborting the study it was decided to operate at some lower setting and discuss the issue of throughput at some future date.

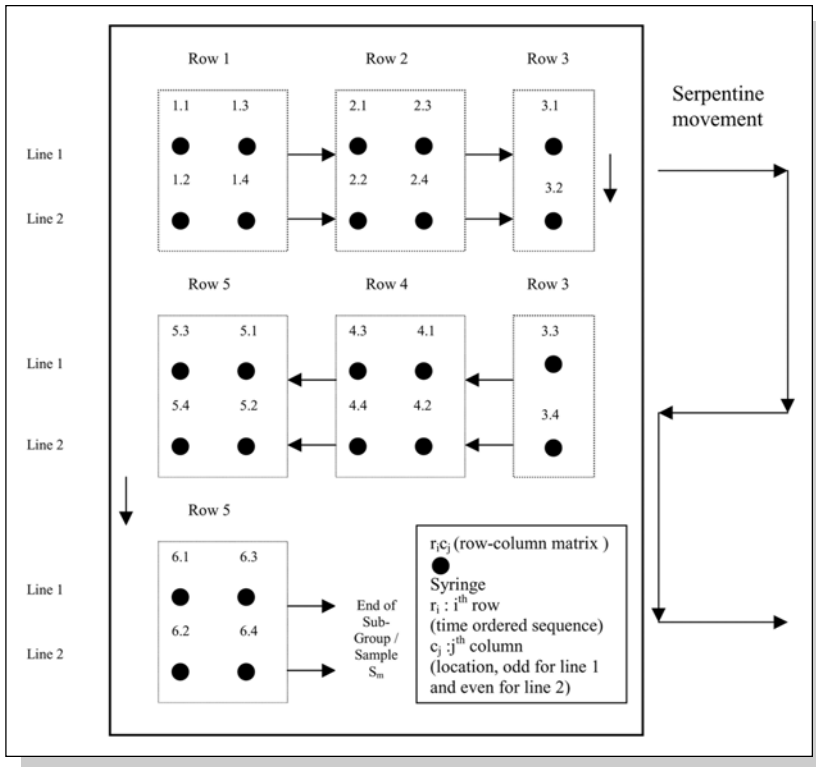


Figure 1. Sampling and serpentine fill pattern.

Third: This machine has two fill lines each with separate hoses, pump, and needle. In two machine strokes, four syringes are filled, and although the data entry table was designed to accommodate two fill lines, the *serpentine filling pattern*, right-left-right movement, was not anticipated - *Figure 1*. This made maintenance of the time-ordered sequence as well as planned sample size somewhat difficult, but not impossible to hold. We had not planned for the serpentine pattern of fill in setting up our original data entry table, consequently we set up an intermediate table for data entry (which was kept on file) and then the final table - *Appendix 2*. This complicated not only data entry, but the pre-weighing and tagging of the syringes as well.

Due to the variation in individual syringes each was weighted prior to fill and after fill. Rubber gloves were worn during data collection at all times and forceps were used in the handling of all syringes in our samples. Filling was performed in an uncontrolled industrial environment at the equipment manufacture's site in Schwabish Hall, Germany.

Data Analysis

Time-Ordered Sequence of all data and Outliers

The pattern of outliers observed in the line graph of all individual observation reveals the effect *time between loading* (TL) had on fill volume and the critical importance of controlling this process variable - *Figure 2*. As noted above, this process variable has no bearing upon the machine capability as loading of the trays is a manual operation. Thus the following original data rows were eliminated from any further statistical analysis: 7, 13, 19, and 25.

When the plotted data were shown to other members of the execution team, on the day following data collection, two team members (one from the vendor and one from the owner) informed the remainder of our group of an additional, unplanned, operator adjustment which occurred after the data collection had already started. This "adjustment" resulted in two data rows containing observations far outside the tolerance limits and more than six standard deviations from the mean. These points were eliminated from further statistical analysis as outliers with a known cause unrelated to the machine capability. Thus, original data rows 1, 2, and 3 were eliminated from further statistical analysis leaving the revised data table (Appendix 2) for final data analysis of the machine capability with 23 rows of data as opposed to the originally planned 30.

A visual examination of this first line graph already suggested some difference between the line-pump-needle configurations - *Figure 2*.

Goodness-of-Fit Testing

With the final data set decided upon our next step was to view the empirical data distribution and form a judgement on model

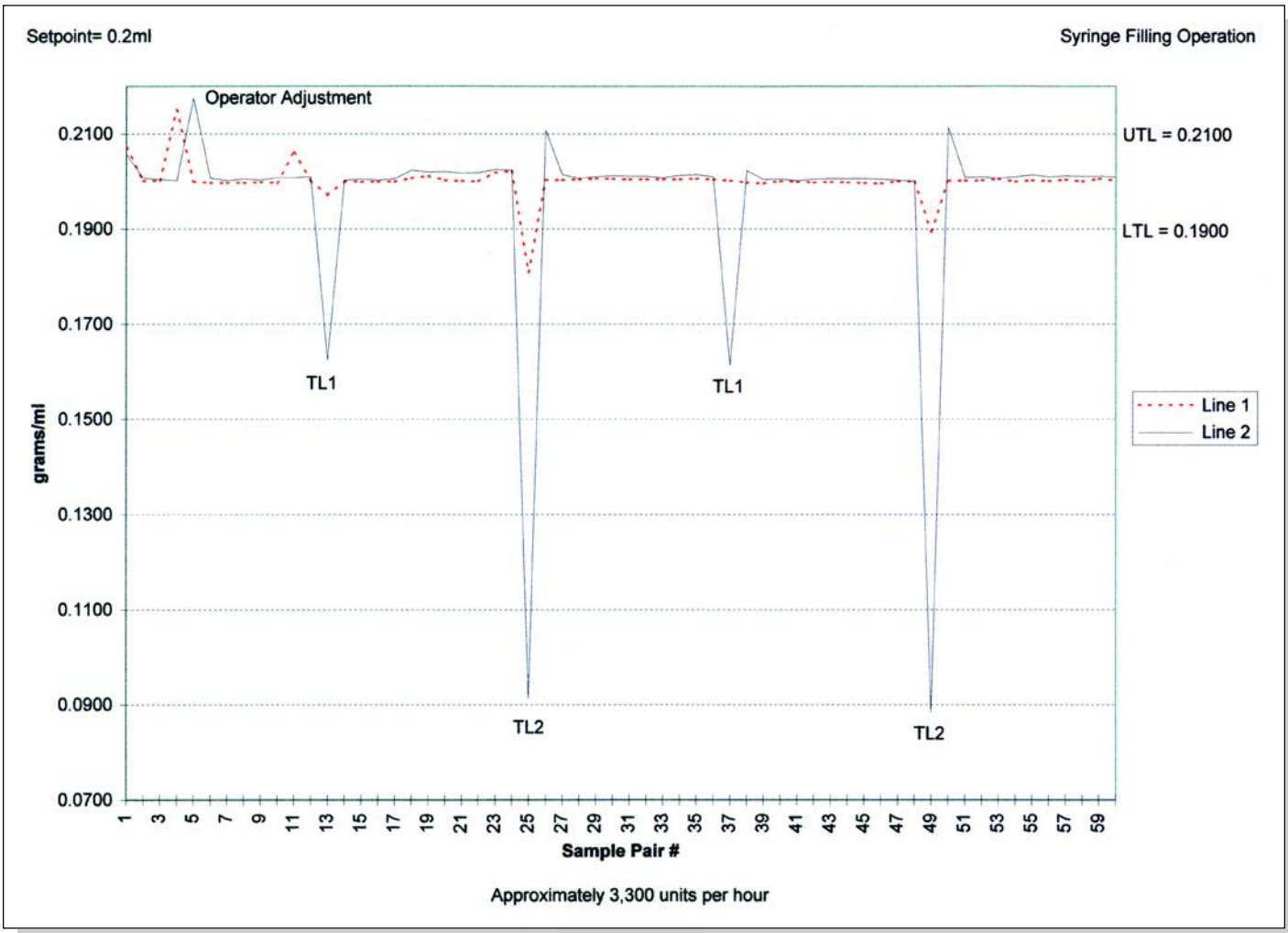
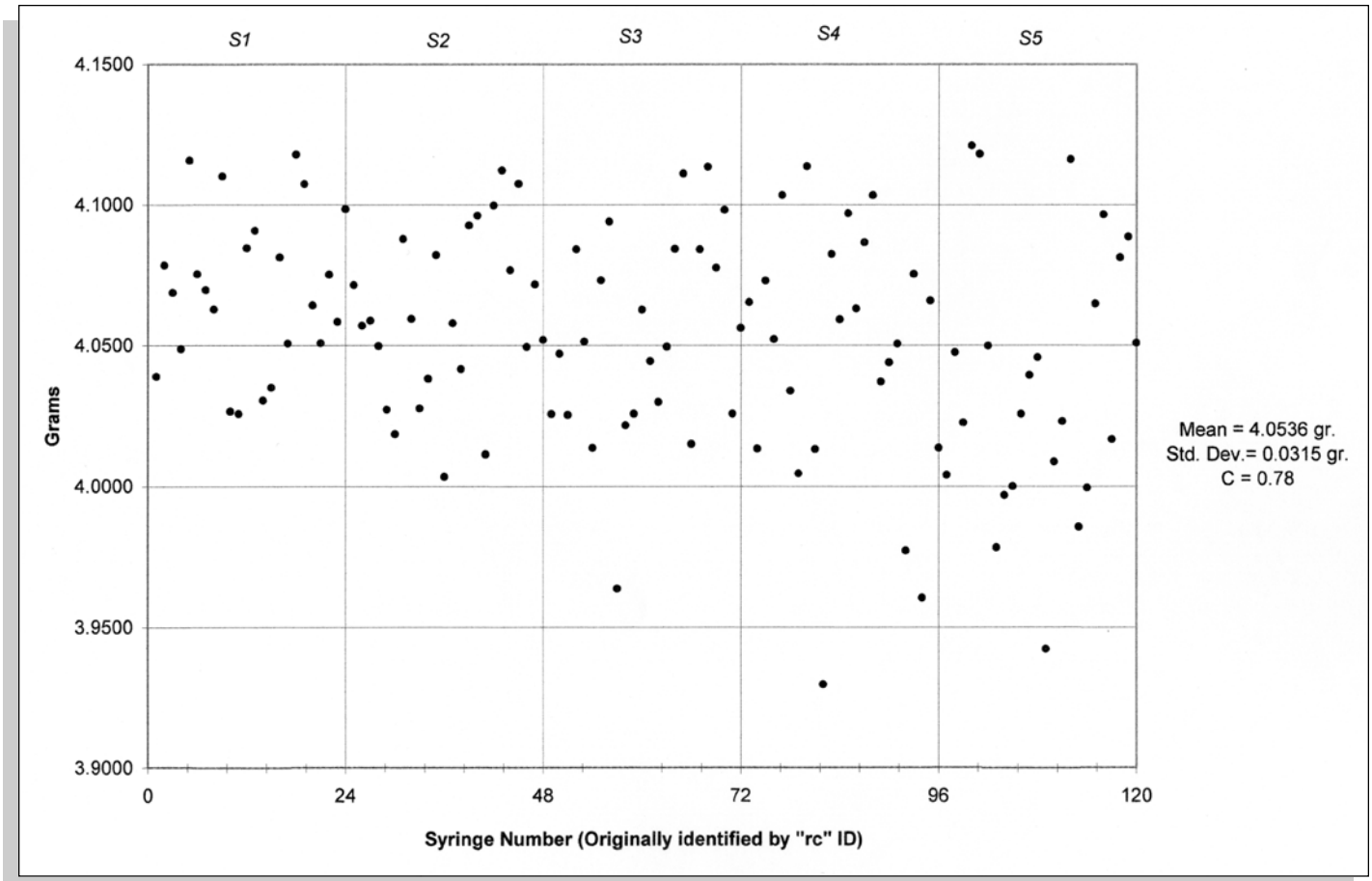


Figure 2. Line graph (all data).



Appendix 1. Scatter diagram and analysis of syringe weight data.

fit, i.e. was the analytical approach valid, and if not, what adjustments if any were to be made. The empirical data distribution may be viewed in a frequency histogram or a cumulative frequency diagram with K-S type confidence bands built about it.[1] The author finds the frequency histogram more useful from a visual and graphical perspective. A visual examination of the frequency histogram suggests again the difference between Line 1 and Line 2 and suggests, given that $\bar{\bar{x}}$ is 0.20068 ml that the combined data are something other than normally distributed, e.g. right skewed suggesting a chi-squared distribution - *Figure 3*. It is not required that the data match the model distribution perfectly.[1,2] (See discussion of model validity below.)

In this project, all data analysis was performed using an Excel spreadsheet and available statistical tables. The assumption of normal distribution was tested using the chi-squared analysis of residuals method described by Conover.[3] This method permits the estimation of population parameters from the sample data with a loss of one degree of freedom for each parameter estimated. Contingency table sizes of 4 and 8 were built with the following results:

The overall fill population (line 1 plus line 2) is not normally distributed. Line 2 is normally distributed but line 1 is not. Line 2 is skewed, as is line 1; however, in testing for goodness of fit using the Chi-Squared test at both classifications of 4 and 8 the null hypothesis (population is normally distributed) is accepted.

The Issue of Sample Size and Data "Grouping"

With the addition of the process variable TL the subgroups (S_1,S_2,S_3, S_4,S_5) of sample size n_g=4 was reduced from (r_i) (c_j) = 24 to (r_i) (c_j) = 20. The calculated size for the subgroup analysis was 22, but was based upon an estimated population variance of 9.0^{-3}; however, since the actual population variation was at least 10 times less (8.9^{-4}), samples of size 20 proved adequate. With subgroup S_1, where data rows 1, 2, and 3 where dropped, we were not so fortunate and consequently data from S_1 were only included in the grouped analysis - *Appendix 3 and Appendix 4*.

An initial review of these data indicated an apparent difference in line-pump-needle configurations which was later confirmed with a simple sign test from which we concluded with more than 99.99% confident that there is a difference between the two lines - *Figure 3*. This difference also is apparent from the 99% CIs built about their respective means - *Appendix 4*. As a result of this analysis we further grouped the data based upon one sample of size 92, and two samples each of size 46 to conduct additional analysis. Given the clear difference between line 1 and line 2, what possible justification could there be for grouping the two lines together? First, each of the two lines must be individually capable of operating within the specified tolerances; and second, the noted statistical variation is not an economic or ethical issue as both "lines" are well within the tolerance limits specified.

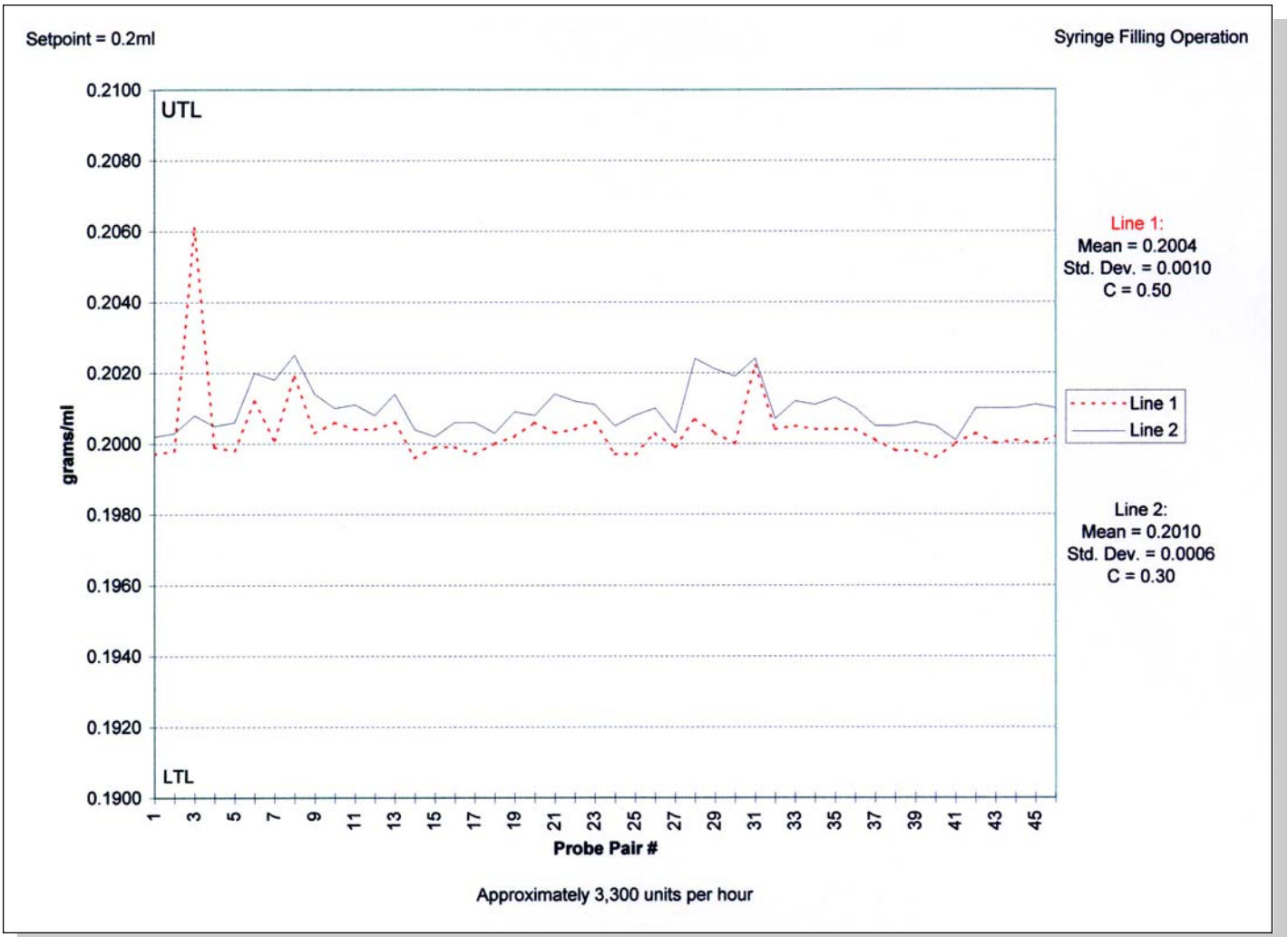


Figure 3. Line graph (revised data).

To maintain a meaningful and valid analysis we varied from the test protocol as follows:

1. The short term machine capability as defined, and indicated on the data entry table, would not be calculated for subgroup one (S_1).

2. The long term machine capability, defined as production of at least 12,000 units would be calculated based upon the new rc matrix. r = 24, c = 4; and, for each line separately.

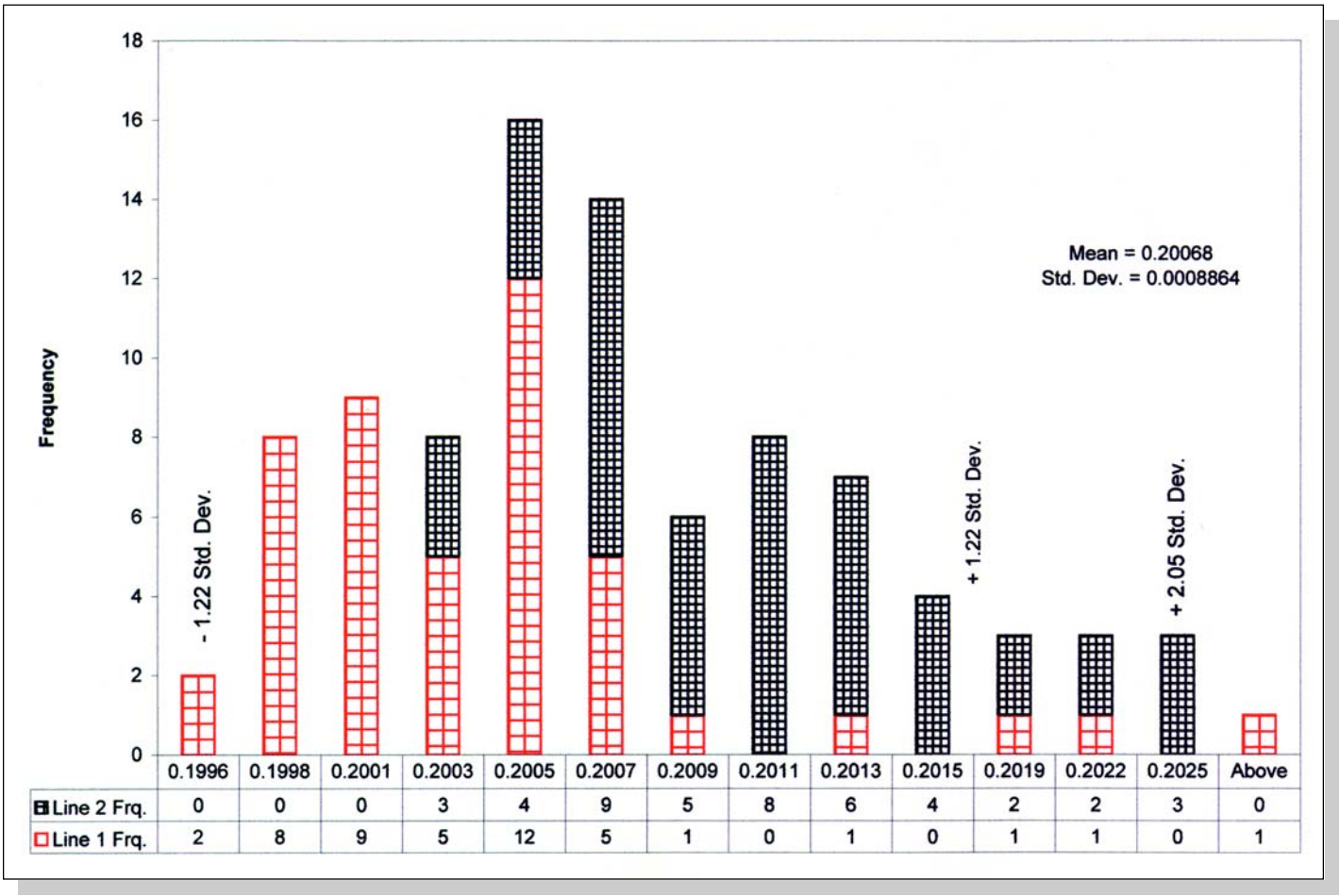
upon the set-point nor was the process normally distributed, consequently an additional factor of conservative estimation was added in that the author prefers the use of kS_m as opposed to either $3\bar{R}/d_2$ or $3S_m$ in calculating the C_{mk} - Appendix 3 and Appendix 4.

Subgroup S_1 was validly eliminated from a separate short term, small sample, analysis because of its size — only 12 — however, it could not by any means be eliminated from other statistical analysis since, unlike the outliers which where clearly attributed to known events not related to the machine's normal operation, there was no explanation for r_3c_1's variation from the mean. This data point was, without explanation, at least five standard deviations from the mean and hence not a chance occurrence. It deserves some consideration if not investigation. C_{mk} compensates for this by looking at both sides. A population distribution? More than 99% of the samples fall between –1.22 and + 2.05 Std. Dev. from the mean on the normal distribution curve, and it is fully 10.5 Std. Dev. to the UTL from the mean and 6.11 Std. Dev. to 0.2061 ml. For these reasons, there are no serious concerns. Thus, seen the normal distribution is an elegant, simple, and adequate model of our machine's operation.

An additional prospective may be gained by viewing the data in light of Tscheyscheff's Theorem. From line one's center (0.2004 ml) to the Upper Tolerance Limit (UTL ,0.2100 ml), it is approximately 9.6 Std. Deviations from the empirical distribution - *Figure 4*. No matter what the distribution no more than 1.1% should fall outside this limit on the high end and 0.9% on the low end. And, from line two's center (0.2010 ml) to the Upper Tolerance Limit (ULT , 0.2100 ml), it is approximately 15 Std. Deviations. No matter what the distribution no more than 0.4% should fall outside this limit on the high end and 0.3% on the low end. No matter what the distribution no more than 1% will be outside the tolerance limits.

The Machine Capability

Given the nature of the machine design (two needles/two fill per stroke) and the population distribution, the author felt some adjustment toward the conservative side of error was in order. From sample to sample, our point estimates of the population



	0.1996	0.1998	0.2001	0.2003	0.2005	0.2007	0.2009	0.2011	0.2013	0.2015	0.2019	0.2022	0.2025	Above
Line 2 Frq.	0	0	0	3	4	9	5	8	6	4	2	2	3	0
Line 1 Frq.	2	8	9	5	12	5	1	0	1	0	1	1	0	1

Figure 4. Frequency histogram (revised data): empirical data distribution.

very cautious estimate of the C_{mk} for this machine and setpoint is: $C_{mk} \geq 2$.

Closing Discussion and Limitations of Protocol

Gains and Losses from Field Modifications to Plan

A test protocol is a guideline and tool to assist in the equipment (or process) testing and the generation of a document package to support manufacturing and regulatory requirements. It is a substantial document having many official signatures and there will always be some apprehension when making field modifications to approved test plans. An experienced team leader or validation engineer will discuss proposed changes with other team members most familiar with the technical aspects and implications first and next consider the organizational and regulatory aspects prior to making any changes. Had our team not responded adequately to the environment (factual and judgmental information) the time-ordered sequence of sampling would have been lost; equipment damage would likely have resulted in a significant delay if not cancellation of the testing altogether, and information important to the process and use of the equipment may not have been captured in a timely manner. With respect to meeting the protocol's stated objectives, nothing was lost. Even the fact that the maximum speed was not tested is not a failure as this is better discussed with the equipment manufacturer as a separate item, and if need be, either the maximum setting changed, or additional testing performed.

The validation team must not permit itself to become slave to the servant, but instead consider all relevant issues as they arise, whenever they arise, and remain flexible to the highest extent possible. Thus viewed the qualification/validation team is an open system responding and adopting to a living environment. Good managers, validation engineers, and teams understand, accept, and act accordingly.

Comments on Line Difference, Height of Bulk Fill Fluid, and Machine Set-point

The lack of adequate fill in both lines after introduction of the process variable TL was attributed primarily to "back-siphoning." This was tested ad-hoc, no data recorded, and found substantially true and might therefore be improved or perhaps eliminated through changing the height of the bulk fill container relative to the filling needle heads. Kinks in lines may have been another contributing factor to this major difference between lines themselves at these observed points.

As stated above from the application of a simple sign test, we are able to conclude with more than 99.99% confidence that there is a difference between the two lines. Such a difference also was suggested by a review of the data (Figures 2 and 3), and confidence intervals built about the line means - *Appendix 4*. In short, the population is not homogenous, and assignable cause is at work here. It may be the result of natural variation in the inside diameter of the fill needles, some other machine variable, or even design, but it is neither of economic nor ethical concern to the process or product of this study.

Original row nr.	Revised row nr.	c1: Line 1	c2: Line 2	c3: Line 1	c4: Line 2	Subsample ID (Syringe ID)	Xbarr	Xmax	Xmin	Rr
r4	r1	0.1997	0.2002	0.1997	***0.2005***	Subsample 1	0.2000	0.2005	0.1997	0.0008
r5	r2	0.1998	0.2003	0.1997	***0.2008***	S_1	0.2002	0.2008	0.1997	0.0011
r6	r3	***0.2061***	0.2008	0.2003	0.2010	0001 - 0024	0.2021	0.2061	0.2003	0.0058
r8	r4	0.1999	***0.2005***	0.1999	0.2003		0.2002	0.2005	0.1999	0.0006
r9	r5	0.1998	0.2006	0.2007	***0.2024***		0.2009	0.2024	0.1998	0.0026
r10	r6	0.2012	0.2020	0.2003	***0.2021***	Subsample 2	0.2014	0.2021	0.2003	0.0018
r11	r7	0.2001	0.2018	0.2000	***0.2019***	S_2	0.2010	0.2019	0.2000	0.0019
r12	r8	0.2019	***0.2025***	0.2022	0.2024	3001 - 3024	0.2023	0.2025	0.2019	0.0006
r14	r9	0.2003	***0.2014***	0.2004	0.2007		0.2007	0.2014	0.2003	0.0011
r15	r10	0.2006	0.2010	0.2005	***0.2012***		0.2008	0.2012	0.2005	0.0007
r16	r11	0.2004	***0.2011***	0.2004	***0.2011***	Subsample 3	0.2008	0.2011	0.2004	0.0007
r17	r12	0.2004	0.2008	0.2004	***0.2013***	S_3	0.2007	0.2013	0.2004	0.0009
r18	r13	0.2006	***0.2014***	0.2004	0.2010	6001 - 6024	0.2009	0.2014	0.2004	0.0010
r20	r14	0.1996	0.2004	0.2001	***0.2005***		0.2002	0.2005	0.1996	0.0009
r21	r15	0.1999	0.2002	0.1998	***0.2005***		0.2001	0.2005	0.1998	0.0007
r22	r16	0.1999	***0.2006***	0.1998	***0.2006***	Subsample 4	0.2002	0.2006	0.1998	0.0008
r23	r17	0.1997	***0.2006***	0.1996	0.2005	S_4	0.2001	0.2006	0.1996	0.0010
r24	r18	0.2000	***0.2003***	0.2000	0.2001	9001 - 9024	0.2001	0.2003	0.2000	0.0003
r26	r19	0.2002	0.2009	0.2003	***0.2010***		0.2006	0.2010	0.2002	0.0008
r27	r20	0.2006	0.2008	0.2000	***0.2010***		0.2006	0.2010	0.2000	0.0010
r28	r21	0.2003	***0.2014***	0.2001	0.2010	Subsample 5	0.2007	0.2014	0.2001	0.0013
r29	r22	0.2004	***0.2012***	0.2000	0.2011	S_5	0.2007	0.2012	0.2000	0.0012
r30	r23	0.2006	***0.2011***	0.2002	0.2010	12097 - 12120	0.2007	0.2011	0.2002	0.0009

Notes:

1. In both Analysis of Data Summary Tables (Appendix 3 and Appendix 4) $\bar{\bar{x}}$ has been used as the estimator for population mean (μ).
2. Observation r_3c_1 = 0.2061 and is 5.73 to 6.12 standard deviations form the mean depending upon whether one uses the grouped or the line data. It appears clear that this is the only point of concern. It seems not to be a random occurrence. Even when we consider that the population is chi-square distributed and not normal… in fact it becomes of increased concern.

Appendix 2. Data summary table: ($r_{23}c_4$: n_g = 4).

Note, that both fill lines were somewhat off the target of 0.20 ml suggesting the possibility that the machine was set on data from one of the lines only; therefore, one possible improvement involving absolutely no costs would be to set the target based upon data from both. Again, this has no negative effect upon the machine's ability to produce within the tolerance limits.

Setting In-Process Control Limits

Although setting in-process control limits was not a stated objective or acceptance criteria in our test plan (see the test protocol in Part 1 of this two part article), it may be seen as a logical conclusion to our data analysis since such control limits wed well with promises of the qualification/validation philosophy of reduced inspection costs and improved control[5] and may be based upon the collected data. In moving from capability testing to in-process control, there is a shift in the statistical analysis from the population to the sample distribution accomplished without losing or sacrificing the requirement that all individual syringe fills fall within the previously defined tolerance limits. The objective of in-process control is to identify and correct assignable causes of variation, which may, if left unchecked, lead to product non-conformance. In-process control limits are based upon the sampling distribution which will *always* be normally distributed. These control limits should not be too narrow. We do not want manufacturing and maintenance groups over-responding to "ghost data" or tampering with a functional system. Nor do we want these limits too wide resulting in an untimely response to actual shifts in the machine's operational characteristics.

In addition to the shift in distribution functions, there is a necessary shift from the machine to the process capability. In our case, this shift may only be accomplished with certain assumptions and we therefore introduce the concept of *hypothetical process capability* into our analysis. If we assume that process variables such as TL, raw materials, and others (Figure 1, Part 1: Partial Fishbone) are under control or do not contribute to variation in fill, then the calculated C_{mk} may be viewed as the process capability and in-process control limits built accordingly.[1]

For a product with substantially the same viscosity, density, and setpoint/fill volume as our test fluid, these limits may be set as follows:[6,7,8]

1. Since we have variable data on a ratio scale we recommend building an $\bar{x}$-Chart and R-Chart. The $\bar{x}$-Chart will detect changes in the machine's aim and the R-Chart will pick up problems with individual syringes.

2. The most economic and appropriate basis for setting these limits is information from n_g = 2 (Appendix 4) and the empirical data - *Figure 4*. We recognize that consideration of operational and process aspects such as the number of

	n	$\bar{\bar{x}}$	$\bar{R}$	S_m	$\bar{R}/d_2$	NPL = $\bar{\bar{x}} \pm 3\ \bar{R}/d_2$	k	NPL = $\bar{\bar{x}} \pm k\ S_m$	C_{mk} $3(S_m)$	$3(\bar{R}/d_2)$	$k\ S_m$	Notes
Grouped full r_ic_j matrix	92	0.20068	0.00124	8.864^{-4}	6.018^{-4}	$\pm 1.805^{-3}$ 0.1989 to 0.2025	3.1	$\pm 2.748^{-3}$ 0.1980 to 0.2035	3.51	5.16	3.39	$S_m > \bar{R}/d_2$
S_1	12	—	—	—	—	—	—	—	—	—	—	Sample size too small for this analysis
S_2	20	0.20113	0.00150	9.989^{-4}	7.285^{-4}	$\pm 2.19^{-3}$ 0.1989 to 0.2033	4.17	$\pm 4.17^{-3}$ 0.1969 to 0.2053	2.96	4.06	2.13	$S_m > \bar{R}/d_2$
S_3	20	0.20077	0.00088	3.813^{-4}	4.274^{-4}	$\pm 1.282^{-3}$ 0.1994 to 0.2021	4.17	$\pm 1.59^{-3}$ 0.1992 to 0.2024	8.07	7.20	5.81	$S_m > \bar{R}/d_2$
S_4	20	0.20014	0.00074	3.468^{-4}	3.594^{-4}	$\pm 1.078^{-3}$ 0.1990 to 0.2012	4.17	$\pm 1.45^{-3}$ 0.1986 to 0.2015	9.48	9.15	6.82	$S_m < \bar{R}/d_2$
S_5	20	0.20066	0.00104	4.418^{-4}	5.051^{-4}	$\pm 1.515^{-3}$ 0.1991 to 0.2022	4.17	$\pm 1.84^{-3}$ 0.1988 to 0.2025	7.05	6.16	5.07	$S_m < \bar{R}/d_2$

$0.20043 \leq \mu_{.99} \leq 0.20093$ (based upon n=92)

Notes:

1. $S_{\bar{x}} = 9.241^{-5}$. It is S_m^2/sqr root of n. $\bar{\bar{x}} \pm 2.66\ (s_{\bar{x}})$. $T_{995,60}$ used to calculate 99% C.I. on μ. T-Distribution used instead of Normal for two reasons: a. pop. is not normally distributed.
2. This operation is slightly off center. As a consequence the C_{mk} is a somewhat better summary statistic than C_m.. $S_m \cong \bar{R}/d_2$ and is an unbiased estimate of the population variance.
3. $n_g = 4$, $d_2 = 2.059$, $A_2 = 0.729$, $D_4 = 2.282$, and $D_3 = 0(8)$.
4. In each case kS_m is a more conservative unbiased estimator than $3\ \bar{R}/d_2$. Vendor software packages sometimes use S_m, without any adjustments, to calculate the C_{pK}.
5. Building of Control Limits ($n_g = 4$):

$UCL_{\bar{x}} = \bar{\bar{x}} + A_2\bar{R}$ and $LCL_{\bar{x}} = \bar{\bar{x}} + A_2\bar{R}$ $\quad$ $\mathrm{UCL}\bar{R} = D_4\bar{R}$ and $\mathrm{LCL}\bar{R} = D_3\bar{R}$

= 0.20068 + (0.729)(0.00124) $\quad$ = 0.20068 - (0.729)(0.00124) $\quad$ = 2.282(0.00124) $\quad$ = (0) (0.00124)

= 0.20158 $\quad$ = 0.19978 $\quad$ = 2.2897^{-3} $\quad$ = 0

Appendix 3. Analysis of data summary table: ($r_{23}c_4$: $n_g = 4$).

	n		$\bar{\bar{x}}$	$\bar{R}$	S_m	$\bar{R}/d_2$	NPL = $\bar{\bar{x}} \pm 3\ \bar{R}/d_2$	k	NPL = $\bar{\bar{x}} \pm k\ S_m$	C_{mk} $3(S_m)$	$3(\bar{R}/d_2)$	$k\ S_m$	Notes
Line 1	46	0.20037	0.20068	0.00086	1.0^{-3}	7.61^{-4}	—	3.5	$\pm 3.500^{-3}$ 0.1969 to 0.2039	3.21	4.22	2.75	$S_m > \bar{R}/d_2$
Line 2	46	0.20100			6.0^{-4}		—		$\pm 2.100^{-3}$ 0.1989 to 0.2031	5.00	3.94	4.29	$S_m < \bar{R}/d_2$

Line 1: $0.20022 \leq \mu_{.99} \leq 0.20052$
Line 2: $0.20091 \leq \mu_{.99} \leq 0.20109$

Notes:

1. $s_{\bar{x}1} = 1.474^{-4}$ $\quad$ $s_{\bar{x}2} = 8.847^{-5}$
2. $n_g = 2$, $d_2 = 1.128$, $A_2 = 1.88$, $D_4 = 3.268$, and $D_3 = 0(8)$.
3. Building of Control Limits ($n_g = 2$):

$UCL_{\bar{x}} = \bar{\bar{x}} + A_2\bar{R}$ and $LCL_{\bar{x}} = \bar{\bar{x}} - A_2\bar{R}$ $\quad$ $\mathrm{UCL}\bar{R} = D_4\bar{R}$ and $\mathrm{LCL}\bar{R} = D_3\bar{R}$

= 0.20068 + (1.88)(0.00086) $\quad$ = 0.20068 - (1.88)(0.00086) $\quad$ = 3.268(0.00086) $\quad$ = (0) (0.00086)

= 0.20230 $\quad$ = 0.19906 $\quad$ = 2.81^{-3} $\quad$ = 0

4. A_2, D_4, and D_3 are constants for using the average range to find control limits for subgroup averages and subgroup ranges (8).

See Part 1 of this article for additional terms and abbreviations.

Appendix 4. Analysis of data summary table: ($r_{46}c_2$: $n_g = 2$).

undetected bad units the operation can afford prior to correction or implications of break-time may drive management to more frequent sampling until additional information is obtained and confidence can be built.

3. Sampling for in-process control must be rational, i.e. occurring at planned intervals with time-ordered-sequence maintained. Samples of size 2, one from each of the "lines," should be drawn about every 10,000 units.

4. The calculated limits are: $UCL_{\bar{x}}$ = 0.20230 ml and $UCL_{\bar{x}}$ = 0.19906 ml. And UCL_R = 0.00281 ml - *Appendix 4*. Statistically, it is a long way from these control limits to the tolerance limits. This is a very favorable position for manufacturing.

5. One may or may not employ narrow-limit gauging,[8-9] e.g. any individual observation greater than 0.2042 ml (more than +4 std. Dev. from mean) or less than 0.1995 ml (more than - 2 Std. Dev. from mean) should trigger an investigation.

Conclusions

We have seen in this case problem that assignable causes to variation may be, and undoubtedly frequently are present, which are of neither economic nor of ethical concern. We have additionally seen that the model assumption of normal distribution may be, and undoubtedly frequently is, violated without invalidating its use to the actual application.

From a theoretical and practical perspective, we have tied the purchase and sales agreement as well as manufacturing specifications, through the capability study design, execution, and analysis to the mission of validation as well as to the fulfillment of manufacturing and regulatory affairs requirements. And, finally, we have explained and demonstrated a clear and meaningful distinction between machine and process capability as well as between short term and long term studies.

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Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Journal of ISPE
January/February, 2001 Vol. 21 No. 1

Building the Perfect Batch

by William N. Gracely, PE, Alan Karner, and Richard E. Parapar

This article addresses one approach to implement the S88 standard software development methodology for building a batch control system allowing users to realize many additional benefits by applying this standard.

Introduction

The ISA S88.01 Standard for Batch Control provides an excellent model for implementing enhanced control capabilities in industrial applications. Process operations and equipment functionality are clearly represented as configurable recipes, phases, units, and control modules in the control system. This architectural structure supports a high level of capability and flexibility. Plant equipment becomes more responsive to both internal and external influences such as abnormal process conditions, operator commands, equipment alarms, material substitutions, and production changes.

Many Batch Management packages provide the necessary tools to create and execute recipe procedures. The process of recipe assembly first requires that a process model be defined which describes the capabilities of the process equipment. These characteristics subsequently dictate the assembly of recipes in terms of units, phases, and associated parameters. In this way, Batch Management provides an important implementation layer of the S88 model.

But in a highly automated manufacturing facility, the Batch Management layer is literally just the tip of the iceberg. Full implementation of an S88-based control system involves designing, programming, and testing hundreds, if not thousands, of distinct software components - *Figure 1*.

Unfortunately, definition of the Batch Management process model does little to advance development of units, phases, and control modules in the control system. Often, the complexity of implementing the S88 architecture presents a significant engineering challenge for the inexperienced control system developer.

This article discusses a development methodology that addresses many of the difficulties associated with implementing S88-based control applications. It was first successfully applied in 1996 for development of Genentech's Clinical Manufacturing Facility (CMF) in South San Francisco, California. This experience demonstrated that by applying a well-structured software development approach, batch control systems can be built in a cost effective manner with higher quality and lower risk.

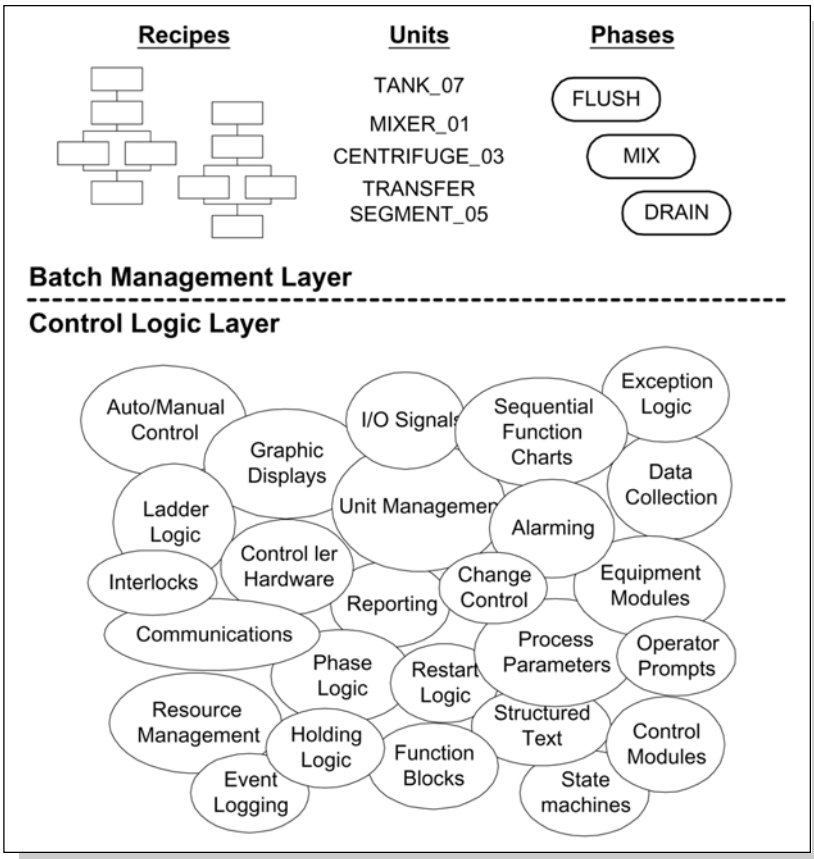

Figure 1. Components of batch management and control logic layers.

CMF Project Overview

Genentech first applied the S(P)88 batch model for the design of its manufacturing control systems in early 1993. In the three subsequent years, dozens of PLC-based, unit-centric S88 control sys-

tems were successfully developed for chromatography, centrifugal, and Tangential Flow Filtration (TFF) protein recovery applications.

Early in 1996, the decision was made that the CMF control application also would be based on the S88 Standard and that all major process operations in the facility would be recipe driven. This would be the company's first attempt at applying S88 for a large-scale multi-product, multi-train application.

CMF Process Application

The new plant consisted of six fully instrumented fermenters (80L, 400L, 2kL, and 12kL scales) and three TFF media transfer skids (400L, 2kL, and 12kL scales). It included fully integrated Clean-In-Place (CIP) and Steam-In-Place (SIP) systems capable of servicing any vessel or transfer line in the plant - *Figure 2*.

The CMF Application required batch recipe procedures to be developed for the following automated process operations:

- CIP and SIP of all fixed tanks, portable tanks, and transfer lines
- Sanitization of TFF transfer units
- Fermentation media batching
- Cell culture growth operations (e.g., inoculation, feeds, perturbations, sampling)
- TFF media exchange, straight pressure, and solera media transfers
- Cell product harvest at both the 2kL and 12kL fermenter vessel scales

More than 47 separate processing units were identified in the facility's equipment infrastructure. They required more than 200 phase logic and 300 control modules to support the process requirements of the facility. Each of these components needed to have detailed specifications written. Control logic had to be programmed and extensively tested. Detailed process graphic and operator interface displays were necessary to support operator supervision and manual operation of the plant. Test procedures had to be prepared so that subsequent project activities such as integrated testing, plant start-up, and validation could begin.

CMF System Architecture

The CMF control system was based on an open distributed control system (DCS) platform with integration of several PLCs. Steam temperature RTD monitoring was implemented in the PLCs and fully integrated with the control logic executing in the DCS. The RBATCH Batch Management package was used for recipe management and execution. Data generated by the control system was collected and archived by a data historian application running on a separate, dedicated server. Information from the historian allowed users to evaluate the operating characteristics of the facility's process operations and equipment, as well as overall product quality.

CMF Development Requirements

Preliminary estimates indicated that more than 20 man-years would be required for designing, developing, and testing the CMF control software. Not surprisingly, this greatly exceeded the project schedule, which allowed only 12 months for the implementation of the control system. The engineering team realized it needed to try and shorten the development cycle by creating a process modeling tool that could capitalize on the highly modular structure of the S88 architecture. It was

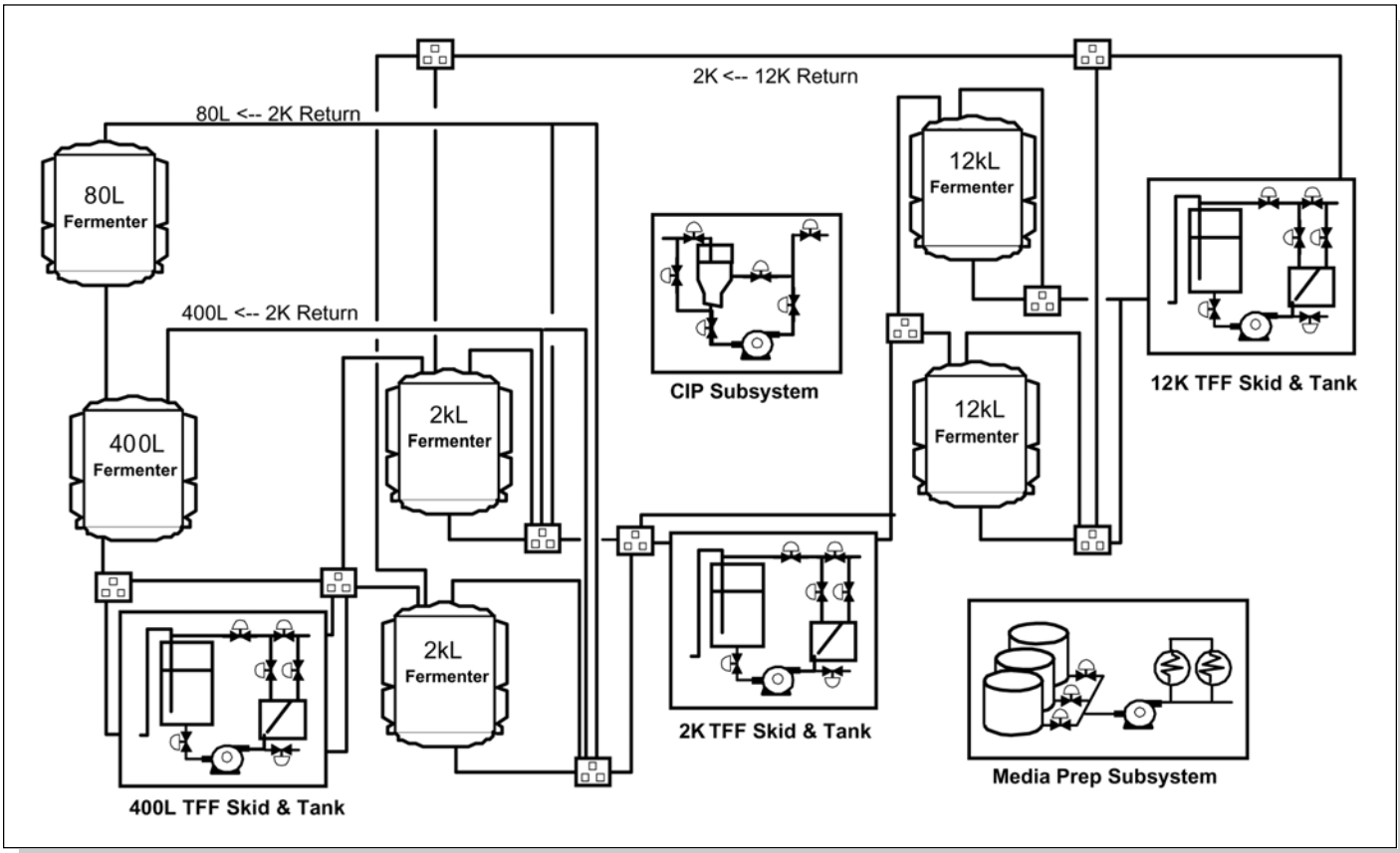

Figure 2. CMF process architecture.

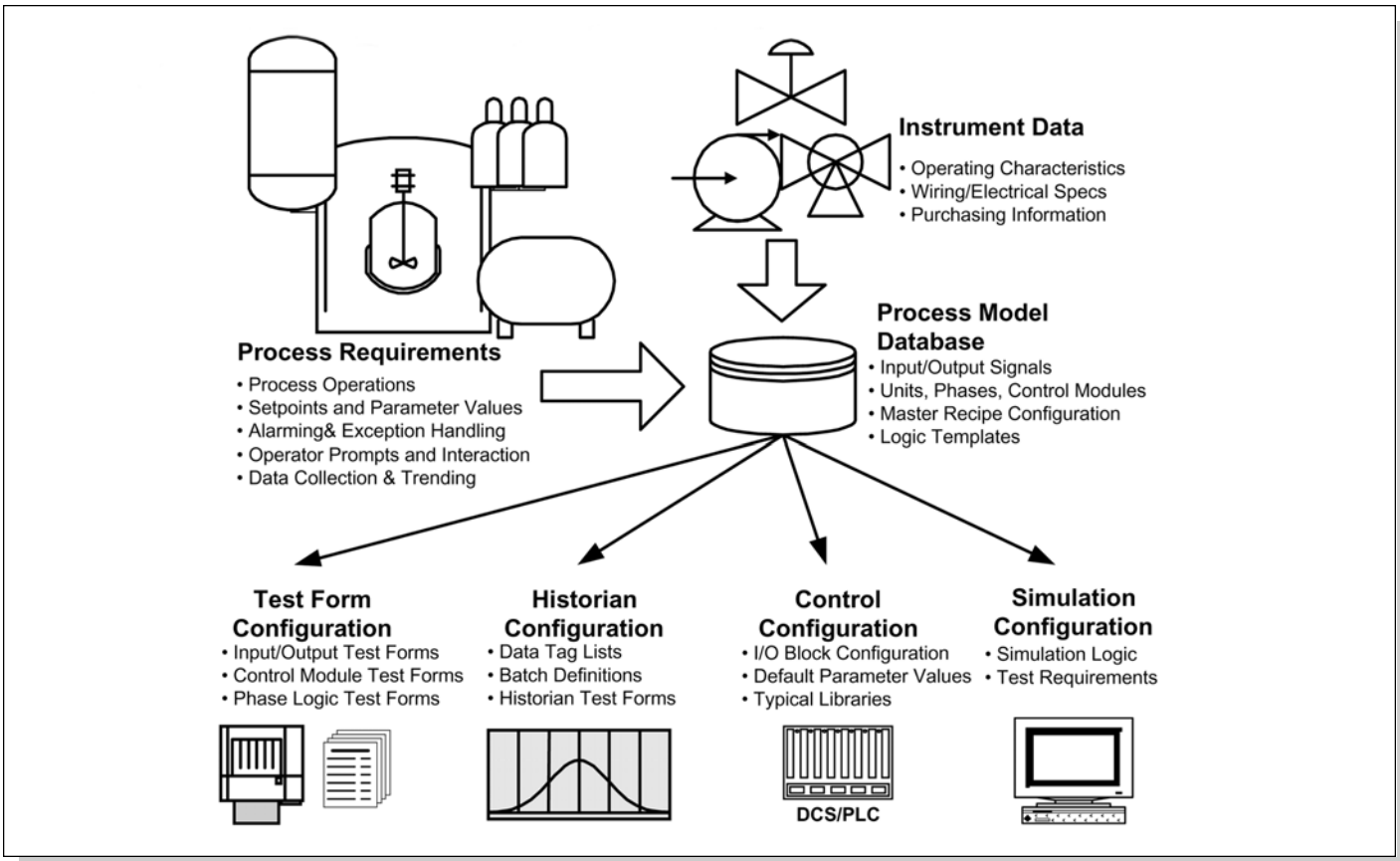

Figure 3. Genentech clinical manufacturing facility - project database components.

believed that using this tool would result in more efficient development and, hopefully, deployment of the control software. The major requirements of the new process modeling tool were to:

- Assist the design team in defining the functional characteristics of the CMF process requirements in terms of S88-based components. The tool would help manage the S88 architecture's inherent complexity by tracking the many units, phases, and control modules, as well as the relationships between these objects in the CMF control application.

- Provide a 'single point of entry' for process modeling and configuration data. The information would be verified at the point of entry, automatically updated, archived, and presented in the appropriate format to the various project personnel requiring access (instrument technicians, control programmers, Quality Assurance test personnel). Change control would efficiently ensure that users always referenced the most current information.

- Facilitate automatic generation of test procedures and reports. Standardized test forms would be developed that, when populated with data from the process model, would help streamline formal system testing and validation.

- Generate the thousands of tag specifications needed to configure the data historian's scanner interface to the DCS. This would allow the data historian's batch model to accurately track the DCS control application without extensive amounts of redundant (and error prone) data entry.

- Support the ability to automatically configure and distribute control logic in the DCS. Process model data, including references to phase logic and control module templates in master libraries, would enable the DCS Control Configuration application to propagate control logic to the DCS controllers.

This last requirement was clearly the most ambitious to fulfill. If successful, it would significantly reduce the amount of time needed for software development. The "hands-off" distribution of control logic throughout the DCS would also greatly enhance the overall quality of the finished system by eliminating many opportunities for programming, copy and paste, and data entry errors.

CMF Process Model Database

The CMF engineers determined that a PC-based relational database application, like Claris FileMaker Pro or Microsoft Access, would satisfy the requirements for the process modeling tool. The "Process Model Database" would serve as the central S88 software design repository. When integrated with DCS configuration application, it also would support automatic creation of the DCS control logic - *Figure 3*.

CMF Process Model

An important activity in the design of the CMF Process Model was identifying common process requirements and equipment characteristics in the plant. From these common requirements and characteristics, detailed specifications for typical software modules were written representing entire classes of operations and equipment in the process model. For example, the

control logic in a Pump Control Module served as a template from which all similar instances of pump control logic in the plant were reproduced.

While many of the major equipment units in the CMF were determined to be similar, if not identical, the decision was made to only develop "typicals" for phases and control modules. The relatively few number of unit instances, compared to phases and control modules, would not result in a significant savings in the programming effort. A decision to support Unit Typicals may be made at some future date. For the CMF Project, Unit Instances were defined directly in terms of Phase Logic and Control Modules Instances, and by association their typicals.

The CMF Application was normalized into its base functional components yielding 59 distinct Phase Logic Typicals and 42 Control Module Typicals out of the 244 and 312 total instances, respectively.

CMF Control Modules

Control Modules offer an object-oriented interface to I/O and the means by which signal conditioning and alarm monitoring are accomplished, as well as the user interface for entering local setpoints or running devices in manual. For example, every valve is issued open/close commands through its control module interface. Although the plant employs both air-to-open and air-to-close valves, operators don't need to consider whether to 'force on' or 'force off' the valve output signal when exercising manual control.

CMT Tag	Description
CMF01001	Fermenter dO2 Controller
CMF01002	Fermenter pH Controller
CMF01003	Fermenter Agitator Controller
CMF01004	Fermenter Overlay Air Flow Controller
CMF01005	Valve Supervisor (16 valve max)
CMF01006	Fermenter Backpressure Controller
CMF01007	Addition Pump w/ calculated feed total
CMF01008	Fermenter Temperature Controller
CMF01009	SIP Temperature/Pressure Controller
CMF01010	Fermenter Volume Indicator
CMF01011	Analog Input Indicator
CMF01012	Proximity Jumper Supervisor (16 max)
CMF01013	Discrete Valve Controller
CMF01014	TFF Membrane TMP Calculation
CMF01015	TFF Feed Flow Controller
CMF01016	TFF Filtrate Pump Controller
CMF01017	Analog Indicator w/ Alarm Delay
CMF01018	TFF Recycle Tank Agitator Controller
CMF01019	TFF Recycle Tank Level Controller
CMF01020	TFF Recycle/CIP Pressure Controller
CMF01021	TFF Recycle/CIP Temp Controller
CMF01022	TFF Chemical Dist Pump Controller
CMF01023	Media Supply Controller
CMF01024	Discrete Device w/ HOA Station
CMF01025	Harvest Filter dP Control Module
CMF01026	CIP Recirc Tank Level Controller
CMF01027	DIW Tank Level Controller
CMF01028	CIP Supply Temperature Controller
CMF01029	CIP Supply Flow/Pressure Controller
CMF01030	CIP Chemical Makeup Controller
CMF01031	Discrete Switch Indicator
CMF01032	ESTOP Monitor
CMF01033	Plant Powerloss Monitor
CMF01034	Analog Selector
CMF01035	Plant Alarm Annunciator
CMF01703	Unit/Equipment Module Supervisor

Figure 4. Control module typical tags.

PLT Tag	Description
PLF01002	CIP4 Skid Server Sequence
PLF01004	Fermenter Class CIP Sequence
PLF01005	Fermenter Pneumatic Test
PLF01007	Fermenter SIP Sequence
PLF01009	Fermenter Antifoam Transfer
PLF01010	Fermenter Addition Transfer
PLF01011	Fermenter Set Environment
PLF01012	Fermenter OUR Perturbation
PLF01013	Fermenter Addition Monitor
PLF01014	Fermenter Sample Monitor
PLF01015	Fermenter Culture Monitor
PLF01018C	2kL/12kL Fermenter Inoculation
PLF01022A	Fermenter Heat Kill – Fill
PLF01022B	Fermenter Heat Kill – Heat
PLF01022C	Fermenter Heat Kill – Drain
PLF01026A	Fermenter Cool Filter (w/ Integrity Test)
PLF01026B	TFF Cool Filter (w/ Integrity Test)
PLF01027	Fermenter Media Batch
PLF01030A	Fermenter A Line Flush Media Filter
PLF01032	TFF Transfer Line CIP Sequence
PLF01034	TFF Drain
PLF01035	TFF Single Pass Flush
PLF01038	TFF Membrane Pressure Hold Test
PLF01039	TFF SIP Sequence
PLF01041	TFF Media Exchange Transfer
PLF01042	TFF Base Clean Sequence
PLF01043	TFF Acid Clean Sequence
PLF01045	TFF Straight Transfer
PLF01047	TFF PBS Flush (Harvest)
PLF01048	TFF Harvest Transfer
PLF01052	TFF Tank PW Rinse
PLF01053	TFF Tank Flush Connect
PLF01054	TFF Tank Flush Disconnect
PLF01055	TFF Tank CIP Sequence
PLF01056	Harvest Filter CIP Sequence
PLF01061	Message Board Prompt Phase
PLF01062	Transfer Panel Jumper Setup
PLF01100	Resource Allocation/Deallocation

Figure 5. Phase logic typical tags.

CMF Phase Logic

One of the core design principles of the CMF Project was the belief that recipes should provide the primary interface for process scientists and engineers to configure and execute process operations via the control system. The intent was to make plant users more responsible for knowing how to build and execute their own recipes. Phase logic in the control system, therefore, serves as one of the fundamental building blocks process scientists and engineers use to build recipe procedures in the Batch Management package.

If recipes are to be user configurable, then recipe phases must be defined at a level that makes sense from a process perspective. Phases should represent, in of themselves, minor process operations in the facility. Examples of process-oriented phases include "Fermenter SIP," "Fermenter Pneumatic Test," and "TFF Harvest Transfer." These phases are defined to be broad in scope, and include the complete sequence of equipment control required to accomplish significant processing steps. Several advantages are realized using this phase design approach.

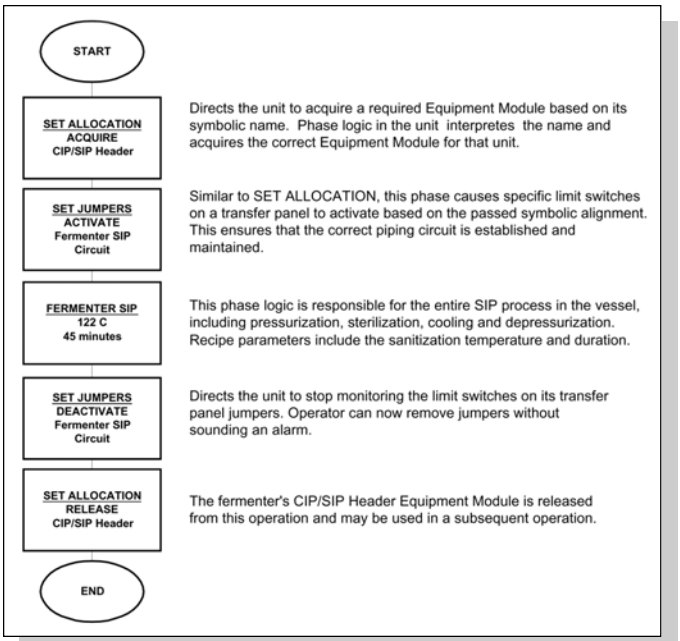

Figure 6. Fermenter SIP recipe example.

- For recipe configuration, larger process phases appear more familiar and are easier to configure for users. Many equipment and operation details don't need to be made visible at the recipe level. For example, the "Fermenter Media Batch" phase allows the user to specify only the major process parameters associated with the batching of a fermenter vessel (e.g., media selection, temperature, transfer volume) without having to assemble the segments of the media transfer sequence using many small phases. Control configuration parameters are implemented at each of the control module, phase logic, and unit levels, but are not made visible at the recipe level unless there is an explicit requirement to change the value from one recipe execution to the next. This approach minimizes the number of recipe parameters and makes phases easier to configure by the user.

- More sophisticated holding and restart logic can be implemented within a larger phase. Combining many small phases in the recipe is more difficult, where limitations in the SFC programming language become problematic. A larger phase, responsible for all the activities in a major process step, is thoroughly familiar with the Equipment and Control Modules that are used in the step. It knows the correct start-up and shutdown sequence, and is better suited for implementing sophisticated exception and holding logic than at the recipe level.

For the CMF application, the implementation of large phases, representing complete segments of major process operations, resulted in smaller recipes. These recipes were easier for users to configure in the Batch Management package, while allowing control programmers to implement more sophisticated control sequences in the controllers.

CMF Recipes

The implementation of large, class-based phases naturally leads to class-based recipes. By developing recipe templates with large phases that describe only the major process steps, the same recipe template can be applied to a wide range of equipment sizes (e.g., 80L, 400L, 2kL, and 12kL).

For example, a single fermenter class SIP recipe successfully addresses the sanitizing requirements of all four 2 kL and 12 kL fermenters in the plant. The same master recipe is used for each vessel, and is made up of only three phase typicals - *Figure 6*.

From the user's perspective, the SIP recipe is very easy to configure and execute because of its class-based design. The SIP Phase Logic in each unit is pre-configured with the parameter values specific to each equipment instance. The recipe ensures that the SIP phases execute in the proper order. This greatly reduces the overall number of recipes required for the CMF Application - *Figure 7*.

Recipes made up of fewer, larger phases have a significant advantage in that the majority of the process sequencing logic executes in the controller, and not in the Batch Management package. The Structured Function Chart (SFC) representation of recipes is often misapplied for implementing detailed sequence programming at the recipe level. This means that recipe execution by the Batch Management package, which typically resides outside the controller, is responsible for coordination of phase starts/stops in a synchronous manner. In any case, interlocks between concurrent phases must be implemented to ensure this happens correctly. Also, larger phases residing in the controller can be executed in manual mode at the Unit level, outside the context of a recipe. This is advantageous during system start-up, as well as during normal operations.

CMF Units and Equipment Modules

The CMF Process Model recognizes the existence of both Units and Equipment Modules. Equipment Modules are an important layer of the S88 model because they allow units to share common resources with other units. As a result, Units are smaller and easier to develop. They become more open to class-based normalization and more reproducible in the process model.

Equipment Modules are functionally equivalent to Units that have only Control Modules and no Phases. This construct allows greater flexibility of equipment grouping in the plant. Control Modules are bundled into a single use, shared equipment resource that can be acquired as needed by Units.

At the recipe's direction, a Phase in the Unit books an

Recipe Tag	Description
RCP01001	400L/2kL/12kL Fermenter Media Batch Recipe
RCP01002	80L Fermenter Media Batch Recipe
RCP01003	400L/2kL/12kL Fermenter Media Line CIP Recipe
RCP01005	400L/2kL/12kL Fermenter Vessel CIP Recipe
RCP01006	80L Fermenter Vessel CIP Recipe
RCP01009	Portable Tank CIP Recipe
RCP01010	TFF Recycle Tank CIP Recipe
RCP01012	2kL/12kL Fermentation Process Recipe
RCP01014	80L/400L Fermentation Process Recipe
RCP01015	400L/2kLTFF Skid Sanitization Recipe
RCP01016	2kL/12kL Fermentation Vessel SIP Recipe
RCP01017	80L/400L Fermentation Vessel SIP Recipe
RCP01018	2kL TFF Harvest Transfer Recipe
RCP01019	400L/2kL TFF Media Exchange Transfer Recipe
RCP01020	400L/2kL TFF Straight Transfer Recipe

Figure 7. Recipe tags.

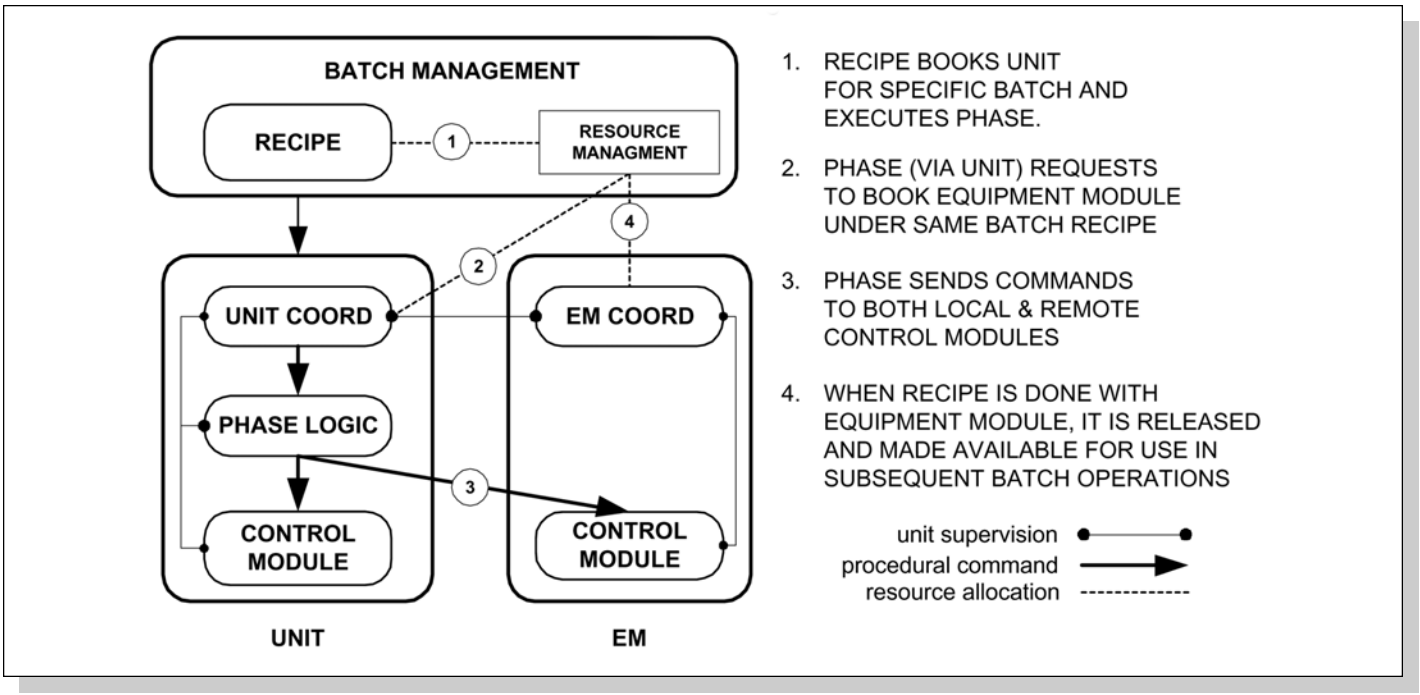

Figure 8. Equipment module acquisition.

Equipment Module for the same batch procedure as the Unit is booked for. This is accomplished in conjunction with the Batch Management package where equipment resource management is performed.

Once the Equipment Module is successfully acquired, Phase Logic in the active Unit can manipulate the Control Modules in the remote Equipment Module. The Equipment Module provides a physical extension of the unit supervision logic in the Unit - *Figure 8*.

In the CMF Application, a common control logic template was applied for all instances of Units and Equipment Modules in the process model. The Unit/Equipment Module changes its characteristics depending on whether it is acquired by Batch Management for recipe phase execution, or by another Unit requesting access to its Control Modules. As an Equipment Module, it provides a valuable service to the acquiring Unit by coordinating command functions and alarm notification between its Control Modules and the Unit's Phase Logic.

An example in the CMF Application of a dual-use Unit/Equipment Module is the TFF Recycle Tank. During media transfer operations between fermenters, the tank functions as a subordinate Equipment Module to the TFF Media Exchange Unit. Later, after being released by the transfer operation, the tank is acquired as a Unit for the CIP Recipe and executes CIP Phase Logic to perform its cleaning sequence - *Figure 9*.

Unit Tag	Description	Function
CIP4	CIP System	UNIT
F1228	2kL Harvest Filters	EM
T1215	400L Fermenter	UNIT
T1215A	400L Fermenter Media Line	UNIT/EM
T1215E	400L Fermenter Inocaulum Line	EM
T1215JM	400L Fermenter Harvest & Recycle Lines	EM
T1215N	400L Fermenter CIP/SIP Header	EM
T1228	2kL TFF Recycle Tank	UNIT/EM
U1221	400L TFF Media Exchange Skid	UNIT
X1225	TFF Acid Distribution Subsystem	EM
X12kL	12kL Media Transfer Subsystem	EM

Figure 9. Unit/equipment module - TFF recycle tank.

CMF Process Model Database

The CMF Process Model Database was constructed to serve as the central S88 software design repository and support automatic creation of the DCS control logic. The overall schema of the Process Model Database is shown in Figure 10.

The first step in creating the database was to define the data layout, or schema, that identifies the significant objects to manage. Based on our knowledge of S88, we knew that objects

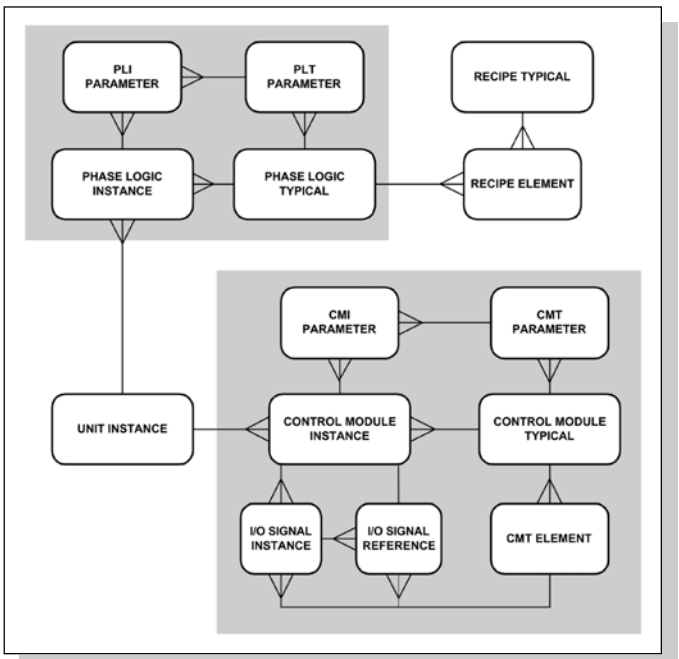

Figure 10. CMF process model database schema.

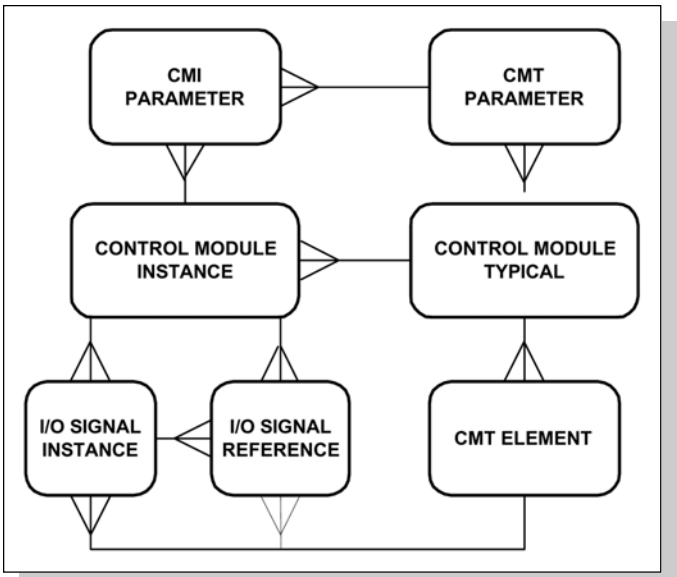

Figure 11. Relationship between control module instances and control module typicals.

such as units, phases, control modules, and I/O signals would be needed. As the schema in Figure 10 illustrates, Unit Instances are composed of Phase Logic and Control Module Instances.

I/O Instances and References

I/O signals are represented in the database by objects called "I/O Instance" objects. Every signal to/from a device or piece of equipment is described using attributes that describe its function and logically associate it with a specific Control Module Instance (CMI).

I/O information includes the Control Processor (CP) and Field Bus Module (FBM) through which the signal is accessed, a detailed description of the signal or device, the high and low signal range, engineering units, and in the case of discrete outputs, whether the signal should be inverted (as for air-to-close devices). Other attributes describe the cabinet, rack, and I/O card where the point is connected to the control system. With this information, detailed wiring tables and calibration test forms are created to help ensure that all signals are properly landed and configured.

In some cases, it is necessary for more than one control module to read the data value of an input signal. An example of this is a pressure transmitter that multiple pressure control-

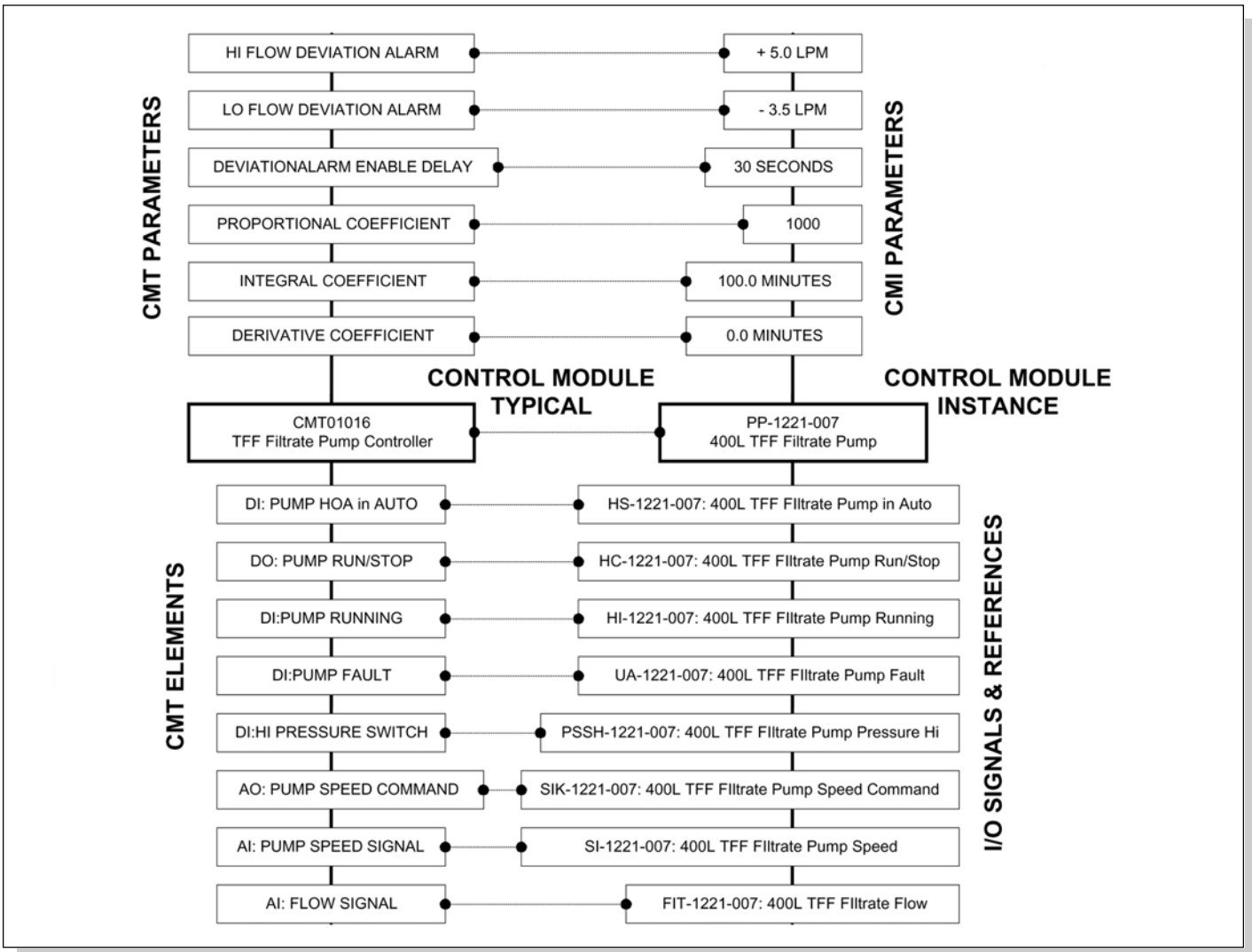

Figure 12. Example CM typical to CM instance propagation.

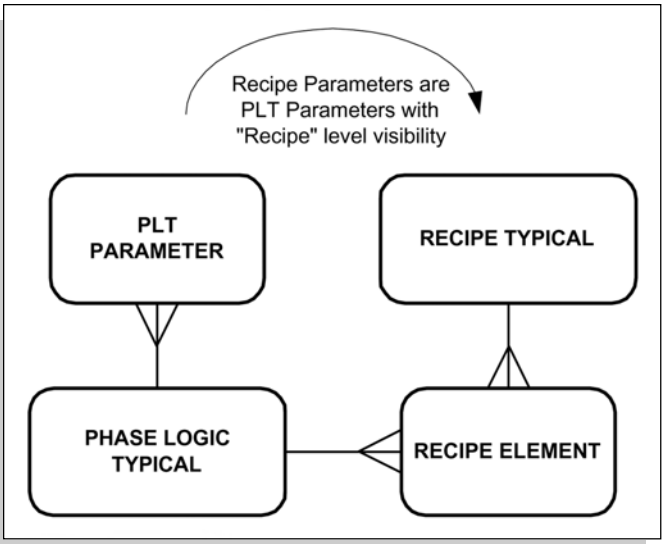

Figure 13. Relationship between recipe typicals and phase logic typicals.

lers read for their process variable. Since the I/O Instance can only "belong" to one Control Module, a data object called an "I/O Reference" is defined. An I/O Reference represents the connection from a Control Module to an I/O Instance belonging to another Control Module. Only input signals are linked by references.

Control Module Typicals, Elements and Parameters

Given that I/O Instances are the components of Control Modules Instances, an equivalent object is required to represent the components of Control Module Typicals (CMTs). These are called the "Elements" of a Control Module Typical. Each CMT Element defines a functional signal interface for a Control Module Typical that an I/O signal will fulfill in a Control Module Instance. In the case of the Pump Control Module, the discrete input signal indicating that the pump is active is represented by the "Pump Running" Element in the Pump Control Module Typical. Either an I/O Instance or I/O Reference can be associated with a CMT Element.

In addition to I/O, Control Modules require configuration parameters to define the runtime behavior of the control logic. Continuing the example, a Pump Control Module has a parameter that defines how long the control logic should wait after starting the pump before enabling its "Loss of Running" alarm. A default value for the parameter is defined in the Control Module Typical, but can be adjusted for each Control Module Instance to filter out nuisance alarms. These parameters associated with Control Module Instances (CMI) and Control Module Typicals (CMT) are called CMI Parameters and CMT Parameters, respectively - *Figure 11*.

The ability to associate I/O signals and parameter values with the functional elements of template-based logic is the foundation for automatically populating controllers with fully configured control logic. Information in the Process Model Database is exported to the DCS configuration application that maps the I/O signal designations and control parameter values onto templates residing in its software library. This allows the configuration application to automatically create control module instances in the designated controllers - *Figure 12*.

Phase Logic Typicals

Phase Logic Typicals are the templates from which Phase Instances are derived. A relationship similar to that between control modules and Control Module Parameters applies for both Phase Logic Instances (PLI) and Phase Logic Typicals (PLT). Phase parameter objects are called PLI Parameters and PLT Parameters, respectively. Again, default values are defined in the library template, and then modified in the instance as necessary.

Recipe Typicals

Recipe Typicals represent the set of phases required to conduct process operations in the plant, like sanitization of a media transfer unit or batching of a fermenter vessel. Recipe typicals correspond to Master Recipes in the S88 model. It is possible to define the characteristics of recipes with Phase Typicals. For process modeling purposes, it is sufficient to view recipes as consisting of only two parts: the header and the procedure. The recipe's header identifies the master recipe by name, description, version number/date, and related information. To keep things simple, the procedure is made up of only phases and not operations. A recipe's procedure can be described by a list of the Phase Typicals referenced in the recipe. This interpretation of recipes, while limited, supports the indication in the recipe of changes to component phases or associated parameters.

Data objects called "Recipe Elements" are analogous to PLT Elements and CMT Elements. They describe the relationship between a Recipe Typical and a specific Phase Typical that the recipe expects to execute in the unit - *Figure 13*. This association allows the Process Model Database to identify PLT Parameters that have their visibility set at the "recipe" level. A list of the parameter configuration requirements can be constructed for each master recipe.

CMF Results

Use of the CMF Process Model Database to design and configure the control application was instrumental in the successful completion of the CMF Project. It took approximately two months to set up and populate the database with information about I/O signal instances and the unit/phase/control module breakdown of the CMF process model. An additional month was needed to integrate export data from the database with the DCS configuration application. Once the database's ASCII-based export files were properly formatted, data transfer to the configuration application worked seamlessly and reliably throughout the project lifecycle. The control software itself required approximately 12 months of detailed Phase Logic and Control Module design and programming.

The final software was extensively tested and verified to be bug free, a significant accomplishment in light of the complexity of the application. The DCS/PLC control system proved capable of executing sophisticated process operations with minimal interaction with plant personnel. Plant operators were consis-

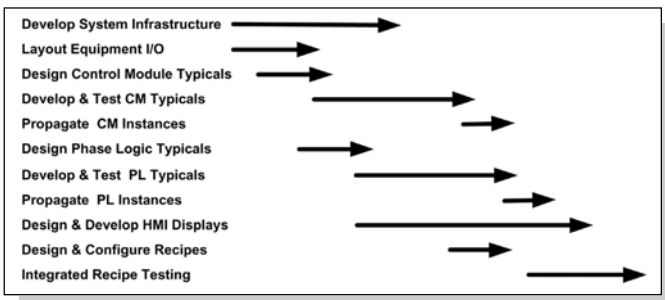

Figure 14. CMF software development schedule.

tently impressed with the capability and reliability of the new control system and pre-licensing 'mock' runs resulted in excellent product yields for the plant scientists.

Several project goals were achieved using the Process Model Database as a tool with which to develop the S88-based control application.

Compression of the Software Development Cycle

Because of S88's inherent modular structure, and the ability of the Process Model Database to effectively track all the software components, it was possible to significantly compress the software development schedule by performing development tasks in a tightly staggered, parallel manner - *Figure 14*.

Control system developers were assigned to different software engineering teams responsible for developing specifications, programming control modules and phase logic, building HMI displays, simulation and wet testing, project documentation, and systems management. Their efforts were coordinated through the Process Model Database and well documented, object-oriented interfaces minimized programming interactions between the different groups.

Increased Responsiveness to Changes in the Requirements

The automated software development mechanism proved very responsive to late process and equipment modifications to the plant's design. In cases where equipment had to be added at the last minute, it was possible to quickly add the instance definition to the Process Model Database and automatically generate new control logic from library typicals.

In other situations, the functionality of existing Control Modules needed to be augmented (e.g., implementing a new control algorithm for all Dissolved Oxygen Controllers). Control Module Typical logic was able to be quickly modified, tested, and redistributed to all instances of the Control Module in the plant. By maintaining the instance-specific configuration parameters in the database, the updated Control Module Instances were deployed and fully functional with no manual programming required. This helped to ensure that the qualification status of tested modules was never compromised.

Improve Efficiency of Validation Process

Comprehensive document and version control ensured that valuable time and resources were not wasted at any point in the project schedule. Development and test personnel relied on the Process Model Database to ensure they always worked with the most current software designs.

The test and validation effort was greatly accelerated. Testing of I/O installation began while Control Module design was not yet complete, and before Phase Logic design even started. Once I/O was verified, testing continued for Control Modules, then Phase Logic, and finally entire Recipe procedures. Automatic generation of test forms permitted the qualification effort to closely track design and development. Effective change management and version control was the key factor in allowing software testing to overlap the design and development efforts for the project.

Conclusion

Implementation of the process modeling tool, which capitalized on the S88 Batch Standard's modular architecture, proved to be instrumental in creating a flexible, capable control system of high quality, in a cost efficient manner, while minimizing the overall risk of project failure.

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1. ANSI/ISA-88-1995- Batch Control Part 1: Models and Terminology, American National Standards Institute/Instrumentation, Systems and Automation Society.

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Editor's Note

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These acronyms were compiled to help engineers understand basic terminology as it applies to the relatively new Biotechnology industry, as well as the more established Pharmaceutical industry.

The complete glossary will be available on ISPE's Web site. It will include definitions of terms used in biology, chemistry, HVAC, manufacturing processes, medicine, materials, metallurgy, regulatory concerns, water treatment, and welding.

Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Journal of ISPE
January/February, 2001 Vol. 21 No. 1

Applied Terminology for the Pharmaceutical Industry

by Michelle M. Gonzalez

Introduction

In a world where expediency in the communi cation of ideas and concepts is the ever so consuming issue, it has become necessary to identify organizations, procedures, techniques, and many other daily qualifiers not by their complete descriptions, but rather by their acronyms. Increasingly, these abbreviations are part of our every day endeavors regardless of what field of work we may be involved in. The problem is that we find ourselves either hearing or using a particular combination of letters that have a precise meaning, but we do not know the meaning or we may have forgotten it. Finding these meanings may be sometimes challenging since they are usually referenced on a very limited basis and in many different places.

In the Biotechnology and Pharmaceutical industries this particular issue becomes more complicated due to the globalization of procedures and regulations in addition to the daily scientific advances involving research, testing, new drug production, new treatments for diseases, and advanced means of drug application.

This acronym list is not meant to be a unique or complete guide useful to every individual involved in this industry, but rather as a "living document" that will be periodically updated to provide a handy reference to scientists, engineers, designers, technicians, owners, contractors and other individuals as they apply to this energetic and still evolving industry. Comments and/or suggestions for widening the scope of this document will be welcome, and should be directed to the author or the ISPE Communications Department.

Section I - Abbreviations and Acronyms

- A -

AAAS	American Association for the Advancement of Science
AABC	Associated Air Balance Council
AAALAC	American Association for the Accreditation of Laboratory Animal Care
AAMA	American Architectural Manufacturers Association
AAMI	Association for the Advancement of Medical Instrumentation
AAPS	American Association of Pharmaceutical Scientists
AASHTO	American Association of State Highway & Transportation Officials
ABC	Association of Biotechnology Companies
ABPI	Association of British Pharmaceutical Industries
ABRF	Association of Biomolecular Resource Facilities
ABS	Acrylonitrile Butadiene Styrene
ACDP	Advisory Committee on Dangerous Pathogens (United Kingdom)
ACGIH	American Conference of Governmental Industrial Hygienists
ACGM	Advisory Committee on Genetic Manipulation (United Kingdom)
ACI	American Concrete Institute
ACI	Alloy Casting Institute
ACIL	American Council of Independent Laboratories
ACP	Acyl Carrier Protein
ACPA	American Concrete Pipe Association
ACS	American Chemical Society
ACTH	Adrenocorticotropic Hormone
ADA	Americans with Disabilities Act
ADAMHA	Alcohol, Drug Abuse, and Mental Health Administration
ADC	Air Diffusion Council
ADME	Absorption, Distribution, Metabolism, and Elimination
ADP	Adenosine Diophosphate
ADR	Adverse Drug Reaction
ADSE	Atmospheric Dust Spot Efficiency (Filter test)
ADSL	Asymmetric Digital Subscriber Line
AFM	Atomic Force Microscopy
AGA	American Gas Association
AGS	American Glovebox Society
AHU	Air Handling Unit
AIA	American Institute of Architects
A.I.A.	American Insurance Association
AIChE	American Institute of Chemical Engineers
AIDS	Acquired Immune Deficiency Syndrome
AISC	American Institute of Steel Construction
AISI	American Iron and Steel Institute
AITC	American Institute of Timber Construction
ALSC	American Lumber Standards Committee

ALUS	Automatic Loading Unloading System
AMCA	Air Movement and Control Association
ANDA	Abbreviated New Drug Application
ANSI	American National Standards Institute
AOAC	The Association of Official Analytical Chemists
APA	American Plywood Association
APCI	Atmospheric Pressure Chemical Ionization
API	Active Pharmaceutical Ingredient
API	American Petroleum Institute
ARI	Air Conditioning and Refrigeration Institute
ARV	Avian Reovirus
ASC	Adhesive and Sealant Council
ASCB	The American Society for Cell Biology
ASCII	American Standard Code for Information Interchange
ASHRAE	American Society of Heating, Refrigerating & Air-Conditioning Engineers
ASME	American Society of Mechanical Engineers
ASPE	American Society of Plumbing Engineers
ASSE	American Society of Sanitary Engineering
ASTM	American Society for Testing and Materials
ATCC	American Type Culture Collection
ATP	Adenosine Triphosphate
ATSDR	Agency for Toxic Substances and Disease Registry
AW	Arc Welding
AWS	American Welding Society
AWWA	American Water Works Association

- B -

BAC	Bacterial Artificial Chromosome
BAS	Building Automation System
BASIC	Beginner's All-purpose Symbolic Instruction Code
BAT	Best Available Control Technology for existing direct dischargers (EPA Regulations)
BCT	Best Conventional Control Technology for existing direct dischargers
BEV	Bovine Enterovirus
BEVS	Vaculovirus Expression Vector System
BFS	Blow/Fill/Seal
BGA	Institute für Arzneimittel des Bundergesungdheitsamtes (German Health Authority)
BGM	Buffalo Green Monkey
BHK	Baby Hamster Kidney cells
BIA	Brick Institute of America
BIOS	Basic Input Output System
BL	Biosafety Laboratory
BLA	Biologics License Application
BMA	British Medical Association
BMS	Building Management System
BOCA	Building Officials and Code Administrators
BOD	Bases of Design
BOD	Biochemical Oxygen Demand
BOD	Biological Oxygen Demand
BP	British Pharmacopoeia
BPC	Bulk Pharmaceutical Chemicals
BPD	Biocidal Products Directive
BPE	Bioprocessing Equipment (ASME National Standard)
BPT	Best Practicable Control Technology for existing direct dischargers (EPA Regulations)
BSC	Biological Safety Cabinet
BSCC	Biotechnology Science Coordinating Committee
BSE	Bovine Serum Albumin
BSE	Bovine Spongiform Encephalopathy ("Mad Cow" disease)
BSI	British Standards Institute
BSL	Biosafety Level
BSO	Biological Safety Officer (NIH Guidelines)
BVD	Bovine Viral Diarrhea
BVDV	Bovine Viral Diarrhea Virus

- C -

CA	Cellulose Acetate
CAA	Clean Air Act
CAB	Cellulose Acetate Butyrate
CABO	Council of American Building Officials
CAMU	Corrective Action Management Unit
CAP	Cellulose Acetate Propionate
CARB	Center for Advanced Research in Biotechnology
CBER	Center for Biologics Evaluation and Research
CCAR	Closed Cycle Air Refrigeration
CCCT	Critical Crevice Corrosion Temperature
CCL	Commodity Control List
CDA	Copper Development Association
CDC	Centers for Disease Control
CDER	Center for Drug Evaluation and Research
CDI	Continuous Deionization
CDRH	Center for Devices and Radiological Health
CE	Corps of Engineers (U.S. Department of the Army)
CEFIC	European Council of Chemical Industries Federation
CEN	Comité Européan des Normes (European Committee for Standardization)
CERCLA	Comprehensive Environmental Response Compensation, and Liability Act
CF	Cresol-Formaldehyde
CFC	Chlorofluorocarbon
CFR	Code of Federal Regulations
CFU	Colony Forming Unit
CGA	Compressed Gas Association
CGAP	Cancer Genome Anatomy Project
cGLP	current Good Laboratory Practice
cGMP	current Good Manufacturing Practice (FDA Regulations)
CHO	Chinese Hamster Ovary
CIA	Chemical Industries Association (UK)
CIMS	Computer Integrated Manufacturing System
CIP	Clean-In-Place
CISC	Complex Instruction Set Computer
CISPI	Cast Iron Soil Pipe Institute
CLEC	Cross-Linked Enzyme Crystals
CLL	Constant Level Loading (Lyophilizer)
CLND	Chemiluminescent Nitrogen Detection
CMC	Carboxymethyl Cellulose
CMC	Chemistry, Manufacturing, and Controls
CMMS	Computerized Maintenance Management System
CMO	Contract Manufacturing Organization
CMU	Cementitious Masonry Unit
CN	Cellulose Nitrate
COD	Chemical Oxygen Demand
COP	Clean Out of Place
COSHH	Control of Substances Hazardous to Health
CP	Cellulose Propionate
CP	Cyclic Polarization
CPCT	Critical Pitting Corrosion Temperature

CPG	Compliance Policy Guides (US-FDA)
CPMP	Committee on Proprietary Medicinal Products
CPSC	Consumer Product Safety Commission
CPU	Central Processing Unit
CPVC	Chlorinated Polyvinyl Chloride
CR	Chloroprene Rubber (**Neoprene**®)
CRO	Clinical Research Organization
CRO	Contract Research Organization
CRSI	Concrete Reinforcing Steel Institute
CS	Casein
CSA	Canadian Standards Association
CSCC	Chloride Stress Corrosion Cracking
CSI	Construction Specifications Institute
CSM	Chlorine Sulphonyl Polyethylene (**Hypalon**®)
CSO	Contract Service Organization
CSRS	Cooperative State Research Service (USDA)
CSVC	Computer System Validation Committee (PhRMA)
CTI	Ceramic Tile Institute
CVMP	Committee on Veterinary Medical Products
CVTR	Constant Volume Terminal Reheat (HVAC)
CWA	Clean Water Act

- D -

DCIC	Dual-Column Ion Chromatography
DCS	Distributed Control System
DDC	Direct Digital Control
DDS	Detailed Design Specification
DDT	Dichloro Diphenyl Trichloroethane
DE	Diatomaceous Earth
DEA	Drug Enforcement Administration
DEL	Design Exposure Limit
DFISA	Dairy and Food Industries Supply Association (E-3-A Standards)
DG	Directorate General (UK)
DHI	Door and Hardware Institute
DHSS	Department of Health and Social Security
DIA	Drug Information Association
DIC	Dairy Industry Committee
DIN	Deutsche Institut f?r Normung
DIW	Deionized Water
DMA	Direct Memory Access
DNA	Deoxyribonucleic Acid
DNAPLS	Dense, Non-Aqueous Phase Liquids
DOC	Department of Commerce
DOE	Department of Energy
DOP	Dioctyl Phthalate
DOP	Dispersed Oil Particulate
DOT	Department of Transportation
DQ	Design Qualification
DRAM	Dynamic Random Access Memory
DRR	Division of Research Resources
DSC	Differential Scanning Calorimetry
DSL	Digital Subscriber Line
DURIP	Defense University Research Initiative Program

- E -

EBRS	Electronic Batch Record Systems
EC	European Community (guidelines for GMP manufacturing)
EC	Ethyl Cellulose
ECACC	European Collection of Cell Cultures
ECLs	Established Cell Lines
ECTFE	Ethylene Chlorotrifluoroethylene (**Halar**®)
EDF	Environmental Defense Fund
EDMS	Electronic Document Management Solutions
EFPIA	European Federation of Pharmaceutical Industries Associations
EFTA	European Free Trade Association
EIA	Electronic Industries Association
EIR	Environmental Impact Report
EJMA	Expansion Joint Manufacturer's Association
ELA	Establishment Licensing Application
ELGs	Effluent Limitations Guidelines
ELISA	Enzyme-Linked Immunosorbent Assay
ELSD	Evaporative Light Scattering Detection
EM	Electron Microscopy
EMEA	European Agency for Evaluation of Medicinal Products
EMF	Electromagnetic Force or Electromotive Force
EMS	Eosinophilia-Myalgia Syndrome
EOQ	European Organization for Quality
EP	Epoxide, epoxy
EP	European Pharmacopeia
EPA	Environmental Protection Agency
EPCRA	Emergency Planning and Community Right-to-know Act
EPDM	Ethylene-Propylene-Diene (**Nordel**®)
EPO	Erythropoietin
EPS	Encapsulated Postscript
ERW	Electric Resistance-Welded (pipe)
ERW	Endotoxin Reduced Water
ESACT	European Society for Animal Cell Technology
ESCA	Electron Spectroscopy for Chemical Analysis
EST	Expressed Sequence Tag
ETFE	Ethylene Tetrafluoroethylene (**Tefzel**®)
EU	European Union

- F -

FAA	Federal Aviation Administration (U.S. Department of Transportation)
FACA	Federal Advisory Committee Act
FAT	Factory Acceptance Testing
FCC	Federal Communications Commission
FCI	Fluid Controls Institute
FDIS	Final Draft International Standard
FEP	Fluorinated Ethylene Propylene
FHA	Federal Housing Administration
FASEB	Federation of American Societies for Experimental Biology
FDA	Food and Drug Administration
FDAMA	Food and Drug Administration Modernization Act
FDLI	Food and Drug Law Institute
FEP	Fluorinated Ethylene Propylene (**Teflon**®)
FIBC	Flexible Intermediate-Bulk Container
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act (EPA Regulations)
FIP	Federal Implementation Program
FISH	Fluorescent In Situ Hybridization
FM	Factory Mutual (Insurance Underwriters)
FPM	Fluorine Rubber (**Viton**®)
FRP	Fiber-Reinforced Plastic
FRP	Fiberglass-Reinforced Plastic
FRS	Functional Requirement Specification
FTIR	Fourier Transform Infrared (spectroscopy)
FTP	File Transfer Protocol
FWPCA	Federal Water Pollution Control Act

- G -

GA Gypsum Association
GAMP Good Automated Manufacturing Practice
GAO General Accounting Office
GCLP Good Control Laboratory Practice
GCP Good Clinical Practices
GDP Good Distribution Practices
GEP Good Engineering Practice
GILSP Good Industrial Large Scale Practice
GLP Good Laboratory Practices
GLSP Good Large-Scale Practice
GMAW Gas Metal-Arc Welding
GMO Genetically Modified Organism
GMP Good Manufacturing Practice (FDA Regulations)
GPM Gallons Per Minute
GPS Global Positioning System
GRP Glass Reinforced Plastic
GSA General Services Administration
GTAW Gas Tungsten-Arc Welding

- H -

HAPs Hazardous Air Pollutants
HAZ Heat Affected Zone
HAZAN Hazard Analysis
HAZOP Hazard and Operability
HAZWOPER Hazardous Waste Operations and Emergency Response (OSHA)
HCFC Hydrochlorofluorocarbon
HCT High Containment Transfer
HDPE High Density Polyethylene
HDS Hydrostatic Design Stress
HEL Human Embryonal Lung cells
HEPA High Efficiency Particulate Air (Filtration)
HEW Health, Education, and Welfare
HFC Hydrofluorocarbon
HFP Hexafluoropropylene
HHS Health and Human Services
HI Hydraulic Institute
HIMA Health Industries Manufacturers Association
HIV Human Immunodeficiency Virus
HMR Hazardous Materials Regulations
HMTA Hazardous Materials Transportation Act
HPB Health Protection Bureau (Canadian equivalent of FDA)
HMW-HDPE High Molecular-Weight High Density Polyehtylene
HPLC High Pressure Liquid Chromatography
HSA Human Serum Albumin
HTF Heat Transfer Fluid
HTML Hyper Text Markup Language
HTS High-Throughput Screening
HTTP Hyper Text Transport Protocol
HVAC Heating, Ventilation, and Air Conditioning
HVI Home Ventilating Institute
HWAC Hazardous Waste Action Coalition
HWM Hazardous Waste Management
HWTC Hazardous Waste Treatment Council

- I -

IAFIS International Association of Food Industry Suppliers
IAMFES International Association of Milk, Food, and Environmental Sanitarians (E-3-A Standards)
IAPI Institute of American Poultry Industries (E-3-A Standards)
IAPMO Informational Association of Plumbing and Mechanical Officials
IBA Industrial Biotechnology Association
IBC Institutional Biosafety Committee (NIH Guidelines)
IBCs Intermediate Bulk Containers
IBRV Infectious Bovine Rhinotracheitis Virus
ICBO International Conference of Building Officials
ICH International Conference on Harmonization
ICLAS International Council on Laboratory Animal Science
IEEE Institute of Electrical and Electronic Engineers, Inc.
IES International Electrophoresis Society
IEST Institute of Environmental Sciences and Testing
IFN Interferon
IFPMA International Federation of Pharmaceutical Manufacturers Association
IIR Isobutene Isoprene (**butyl**) Rubber
IMB Irish Medicines Board
IMP Investigational Medicinal Product
IND Investigational New Drug
INN Investigational Nonproprietary Name (committee of WHO)
IOM Institute of Medicine
IPEA International Pharmaceutical Excipients Auditing
IPEC International Pharmaceutical Excipients Council
IQ Installation Qualification
IRB Institutional Review Board
ISA Instrument Society of America
ISDN Integrated Service Digital Network
ISO International Organization for Standardization
ISP Internet Service Provider
ISPE International Society for Pharmaceutical Engineering
ITA International Trade Administration
ITG Inspection Technical Guides (FDA)
ITIC International Toxicology Information Center
IUCLID International Uniform Chemical information Database
IUPAC International Union of Pure and Applied Chemistry
IVD In Vitro Diagnostic

- J -

JIT Just In Time
JPEG Joint Photographic Experts Group

- K -

Kb Kilobase
KB Kilobit
KHz Kilohertz

- L -

LAER Lowest Achievable Emission Rates
LAF Laminar Air Flow
LAL Limulus Amoebocyte Lysate
LAN Local Area Network

LAT	Loading Accumulation Table
LCM	Lymphocytic Choriomeningitis virus
LDPE	Low Density Polyethylene
LDRs	Land Disposal Restrictions
LEL	Lower Explosive Limit
LHM	Liquid Handling Module (Chromatography)
LIMS	Laboratory Information Management System
LLDPE	Linear Low-Density Polyethylene
LPM	Liters Per Minute
LUST	Leaking Underground Storage Tanks
LVP	Large Volume Parenteral
LYO	Lyophilizer (freeze dryer)

- M -

MAb	Monoclonal Antibody
MACT	Maximum Achievable Control Technology for *existing* major sources of HAPs
MACT	Maximum Achievable Control Technology for *new* major sources of HAPs
MAIT	Minimum Auto-Ignition Temperature
MAP	Mouse Antibody Production
MBMA	Metal Building Manufacturer's Association
MB	Megabit
MCA	Medicines Control Agency, (British equivalent of FDA inspectors)
MCAA	Mechanical Contractors Association of America
MCB	Master Cell Bank
MCC	Motor Control Center
MCLs	Maximum Contaminant Levels
MCLGs	Maximum Contaminant Level Goals
MCMV	Mouse Cytomegalovirus
MEIR	Master Environmental Impact Report
MF	Melamine Formaldehyde
MF	Micro Filtration
MHz	Megahertz
MIE	Minimum Ignition Energy
MIL	Military Standardization Document (U.S. Department of Defense)
MIPS	Millions of Instructions Per Second
MKT	Mean Kinetic Temperature
ML	Manufacturer's License
MMPs	Matrix Metalloproteinases
MMS	Maintenance Management System
MoAb	Monoclonal Antibody
MPW	Medical Pathological Waste
MRA	Mutual Recognition Agreement
MSDS	Material Safety Data Sheet
MSS	Manufacturers Standardization Society
MTV	Mouse Thymic Virus
MVM	Minute Virus of Mice

- N -

NAAQS	National Ambient Air Quality Standards (EPA Regulations)
NAD	Nicotinamide Adenine Dinucleotide
NADA	New Animal Drug Application
NARMS	National Antimicrobial Resistance Monitoring System
NAS	National Academy of Sciences
NBC	National Building Code
NBE	New Biological Entity
NBR	Nitrile (**Butadiene**) Rubber
NBS	National Bureau of Standards (U.S. Department of Commerce)
NCCLS	National Committee for Clinical Laboratory Standards
NCE	New Chemical Entity
NCI	National Cancer Institute
NCMA	National Concrete Masonry Association
NDA	New Drug Application
NDE	New Drug Entity
NDR	Nondispersive Infrared Analysis
NEBB	National Environmental Balancing Bureau
NEC	National Electrical Code
NECA	National Electrical Contractors Association
NEMA	National Electrical Manufacturers Association
NEPA	National Environment Policy Act
NESHAPs	National Emission Standard for Hazardous Air Pollutants
NF	National Formulary
NFPA	National Fire Protection Association
NHLA	National Hardwood Lumber Association
NIH	National Institute of Health
NIOSH	National Institute for Occupational Safety and Health
NIR	Near Infrared (spectroscopy)
NIST	National Institute of Standards and Technology
NLM	National Library of Medicine
NME	New Molecular Entity
NMRS	Nuclear Magnetic Resonance Spectroscopy
NORMs	Natural Occurring Radioactive Materials
NPDES	National Pollutant Discharge Elimination System (EPA)
NPDWR	National Primary Drinking Water Regulations (FDA)
NPL	National Priorities List
NPS	Nominal Pipe Size
NPT	National Pipe Thread
NSF	National Science Foundation
NSPS	New Source Performance Standards for new direct dischargers (EPA Regulations)
NTIS	National Technical Information Service
NTU	Nephelometric Turbidity Unit

- O -

OAC	Oxygen-Arc Cutting
OC	Oxygen Cutting
OCPSF	Organic Chemicals, Plastics, and Synthetic Fiber
OCR	Optical Character Recognition
OEL	Occupant Exposure Limit
OEL	Operator Exposure Level
OEM	Original Equipment Manufacturer
OHER	Office of Health and Environmental Research (DOE)
OMB	Office of Management and Budget
OOS	Out Of Specification
OPP	Office of Pesticides Programs
OPTS	Office of Pesticides and Toxic Substances
OQ	Operating Qualification
ORA	Office of Regulatory Affairs
ORDA	Office of Recombinant DNA Activities (NIH Guidelines)
ORO	Office of Regional Operations
OSD	Oral Solid Dosage
OSHA	Occupational Safety and Health Administration
OSPRA	Oil Spill Prevention and Response Act

OTC	Over The Counter (Medicine)

- P -

PA	Polyamide
PAB	Pharmaceutical Affairs Bureau
PAC	Plasma Arc Cutting
PAGE	Polyacrylamide Gel Electrophoresis
PAI	Pre Approval Inspection
PAO	Polyalphaolefin
PAR	Proven Acceptable Range
PB	Polybutylene
PB – ECL	Performance Based – Exposure Control Limits
PB – OEL	Performance Based – Occupational Exposure Limits
PC	Polycarbonate
PCI	Prestressed Concrete Institute
PCR	Polymerase Chain Reaction
PCTFE	Polychlorotrifluoroethylene (**Kel-F®**)
PDA	Parenteral Drug Association
PDAP	Polydiallyl Phthalate
PDF	Portable Document Format (Adobe®)
PDI	Plumbing and Drainage Institute
PDUFA	Prescription Drug User Fee Act
PE	Polyethylene
PEC	Chlorinated Polyethylene
PEEK	Polyaryl Ether Ether Ketone
PEG	Polyethylene Glycol
PEI	Porcelain Enamel Institute
PEL	Permissible Exposure Limits
PETP	Polyethylene Terephthalate
PF	Phenol-Formaldehyde
PFA	Perfluoroalkoxy resin (**Teflon®**)
PFD	Process Flow Diagram
PhRMA	Pharmaceutical Research and Manufacturers of America (formerly PMA)
PHS	Public Health Service
PI	Principal Investigator (NIH Guidelines)
PIB	Polyisobutylene
PIC	Pharmaceutical Inspection Convention (Europe)
PICS	Pharmaceutical Inspection Cooperation Scheme
PID	Piping and Instrumentation Diagram
PL	Product License (for a biological)
PLA	Product License Application
PLC	Programmable Logic Controller
PM	Preventive Maintenance
PMA	Pharmaceutical Manufacturers Association (see PhRMA)
PMMA	Polymethyl Methacrylate
PMP	Preventative Maintenance Program
POM	Polyoxymethylene (**Kematal®**)
POTW	Publicly Owned Treatment Works
POU	Point Of Use
PP	Personnel Protection (insulation)
PP	Polypropylene
PPE	Personal Protection Equipment
PPMV	Parts Per Million Volume
PPS	Polyphenylene Sulfide
PPVE	Perfluoropropylvinylether
PQ	Performance Qualification
PREN	Pitting Resistance Equivalent Number
PS	Polystyrene
PSD	Prevention of Significant Deterioration of air quality permit (EPA Regulations)
PSES	Pretreatment Standards for Existing Sources (EPA Regulations)
PSNS	Pretreatment Standards for New Sources (EPA Regulations)
PTFE	Polytetrafluoroethylene (**Teflon®**)
PTO	Patent and Trademark Office
PUR	Polyurethane
PVAC	Polyvinyl Acetate
PVAL	Polyvinyl Alcohol
PVB	Polyvinyl Butyral
PVC	Polyvinyl Chloride
PVCA	Polyvinyl Chloride Acetate
PVDC	Polyvinylidene Chloride
PVDF	Polyvinylidene Fluoride (**Kynar®**, **Sygef®**)
PVF	Polyvinyl Fluoride
PVK	Polyvinyl Carbazol
PVM	Pneumonia Virus of Mice
PW	Purified Water

- Q -

QA	Quality Assurance (organization)
QC	Quality Control (organization)
QP	Qualified Person
QSIT	Quality Systems Inspection Technique (used in medical devices)

- R -

Ra	Arithmetic Average Roughness
RAC	Recombinant DNA Advisory Committee (NIH Guidelines)
RACT	Reasonably Available Control Technology
RAPS	Regulatory Affairs Professionals Society
RCRA	Resource Conservation and Recovery Act (EPA Regulations)
rDNA	recombinant DNA
RF	Radio Frequency
RFB	Rotary Fluidized-Bed
RFI	Radio Frequency Interference
RFLP	Restriction Fragment Length Polymorphism
RH	Relative Humidity
RISC	Reduced Instruction Set Computer
RMP	Risk Management Planning
RMS	Root Mean Square
RNA	Ribonucleic Acid
RO	Reverse Osmosis
RSD	Relative Standard Deviation
RTP	Rapid Transfer Port
RTP	Reinforced Thermoset Plastic

Continued on page 52.

- S -

SAL	Sterility Assurance Level
SAN	Styrene-Acrylonitrile
SAT	Site Acceptance Testing
SAW	Submerged Arc Welding
SB	Styrene-Butadiene
SBC	Southern Building Code or Standard Building Code
SBCCI	The Southern Building Code Congress International
SBV	Split Butterfly Valve
SCADA	Supervisory Control And Data Acquisition
SCAQMD	South Coast Air Quality Management District
SCIC	Single-Column Ion Chromatography
SCID	Severe Combined Immunodeficiency (bubble-boy

	syndrome)
SCSI	Small Computer Systems Interface
SDI	Steel Deck Institute
SDLC	System Development Life Cycle
SDP	Sterile Drug Product
SEM	Scanning Electron Microscopy
SGML	Standardized General Markup Language
S-HTP	Secure Hypertext Transfer Protocol
Si	Silicone
SI	Système Internationale (system of measurement)
SIM	Society for Industrial Microbiology
SIP	Steam In Place
SIP	Sterilize In Place
SISPQ	Strength, Identity, Safety, Purity, or Quality
SMACNA	Sheet Metal and Air Conditioning Contractors National Association
SMAW	Shielded Metal-Arc Welding
SMO	Site Management Organization
SMTP	Simple Mail Transfer Protocol
SOCMA	Synthetic Organic Chemical Manufacturers Association
SOP	Standard Operating Procedure
SPC	Statistical Process Control
SPCC	Spill Prevention and Countermeasures Control
SQL	Structured Query Language
SSPMA	Sump and Sewage Pump Manufacturer's Association
STL	Safety Toxic Level
STS	Sequence Tagged Site
SUPAC	Scale-Up and Post-Approval Changes
SVP	Small Volume Parenteral

- T -

TAGMK	Tertiary cultures of African Green Monkey Kidney cells
TCA	Tissue Culture Association
TCLP	Toxicity Characteristic Leaching Procedure
TCM	Tissue Culture Medium
TCP/IP	Transmission Control Protocol/Internet Protocol
TDD	Trans-dermal Drug Delivery (product)
TDS	Total Dissolved Solids
TFE	Tetrafluoroethylene (**Teflon**®)
TG	Thermogravimetry
TIG	Tungsten Inert Gas (welding process)
TIMA	Thermal Insulation Manufacturers Association
TIS	Total Ionized Solids
TLV	Threshold Limit Value
TNKase	Tenecplase
TNF	Tumor Necrosis Factor
TNT	Tumor Necrosis Therapy
TOC	Total Organic Carbon
TOP	Turn Over Package
TPA	Tissue Plasminogen Activator
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act (EPA Regulations)
TWA	Time-Weighted Average

- U -

UAT	Unloading Accumulation Table
UF	Ultra Filtration
UF	Urea-Formaldehyde
UFAS	Uniform Federal Accessibility Standards
UHMWPE	Ultrahigh-Molecular-Weight Polyethylene
UL	Underwriters Laboratories (Insurance Underwriters)
ULDPE	Ultra Low-Density Polyethylene
ULPA	Ultra Low Penetration Air filters
UNS	Unified Numbering System (Metallurgy)
UP	Unsaturated Polyester
UPS	Uninterruptible Power Supply
URS	User Requirement Specification
USAN	United States Adopted Names
USB	Universal Serial Bus
USDA	United States Department of Agriculture (E-3-A Standards)
USP	United States Pharmacopeia
USPHS	United States Public Health Service (E-3-A Standards)

- V -

VAC	Volts, Alternating Current
VAV	Variable Air Volume
VEAs	Vasopermeation Enhancement Agents
VCM	Vinyl Chloride Monomer
VCT	Vinyl Composition Tile
VDC	Vinylidene Chloride
VFD	Variable Frequency Drive (speed)
VHP	Vaporized Hydrogen Peroxide
VMD	Veterinary Medicines Directorate (UK)
VOC	Volatile Organic Compound
VPHP	Vapor Phase Hydrogen Peroxide
VRAM	Video Random Access Memory
VTAs	Vascular Targeting Agents

- W -

WAN	Wide Area Network
WCB	Working Cell Bank
WFI	Water For Injection
WHO	World Health Organization
WIP Lab	Work In Progress Laboratory

- X -

XPS	X-ray Photoelectron Spectroscopy

- Y -

YAC	Yeast Artificial Chromosome

About the Author

Michelle M. Gonzalez is the Engineering/Quality Manager at Fluor Daniel, South San Francisco, CA. She has nearly 35 years of experience in facilities design and engineering. Since relocating to the US in 1965, she has held positions of increasing responsibility in mechanical engineering with firms such as Shell Oil, Kaiser Engineers, Bechtel Corporation, and Fluor Daniel. For the last 15 years, she has focused her professional expertise in the pharmaceutical and biotechnology industries. Gonzalez holds an MS in architecture from the Pontificia Universidad Javeriana, in Bogota, Colombia. She is a lecturer at the Stanford School of Engineering, member of the ISPE Baseline® Biotech Guide Task Team, and ASME BPE subcommittees on dimensions and tolerances, and surface finishes. She also has been a speaker and active member of ISPE for the last 10 years.

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Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Journal of ISPE
January/February, 2001 Vol. 21 No. 1

Leak Testing of Isolator Half-Suits and Waste Containers

by Thomas P. Burns

This article illustrates the use of a specially designed inflation plate and a modified pressure can to ammonia test isolator half-suits for ammonia leaks using a new method instead of the traditional 'upside down' method. It also discusses the creation of a special air inlet connector in conjunction with the modified pressure can that will allow ammonia testing of isolator waste containers.

Introduction

With an increased use of isolators in manufacturing operations and sterility testing laboratories, there is an urgency to ensure integrity of these units and their components. While there has been an effort to improve the methods used to test the integrity of isolator canopies and gloves, there has been minimal noted work on the testing of half-suits and waste containers. Historically, leak testing these two components has been inconvenient at best. The current standard methods for testing half-suits and waste containers are as follows:

1. For half-suits, one suit is installed in the isolator upside down (head on the floor), then a bottle of ammonium hydroxide is opened inside the isolator. When the isolator is saturated with the ammonia vapor, the inverted suit is checked with a yellow 'ammonia test' cloth for leaks. (These special cloths change color from yellow to green when exposed to ammonia vapor. They are frequently used as a tool to search for holes/leaks in isolator canopies.) The problems here are (a) the suit to be tested is in an inconvenient location, (b) the suit is not completely extended, (c) the inverted suit is difficult to purge of ammonia vapor, (d) only one suit at a time can be tested, and (e) the workstation is unavailable for cleaning, etc. while testing is being performed. To test a second suit, the ammonia vapor must be purged from the isolator, the inverted suit placed into the correct position, the second suit inverted, and the ammonia steps repeated. This is very time consuming, since it takes an hour or more to purge the ammonia from the isolator and the half-suit.

2. For waste containers, a bottle of ammonium hydroxide is opened inside the workstation isolator. When the isolator is saturated with ammonia vapor, a waste container is connected to the isolator via Double Port Transfer Entry (DPTE) - a type of sterile door for isolators, and the waste container lid removed. The container is then checked with a yellow test cloth for leaks. The problems here are (a) the waste container is in an inconvenient location under the isolator, (b) it is not completely extended, (c) the container is difficult to purge of ammonia vapor, and (d) the workstation is unavailable (must be non-sterile) during leak testing.

Phase I: Air Pressure Decay/ Visual Inspection

The first attempt to improve these processes was to find a way to fully inflate the suits and the waste containers.

Half-Suits

An inflation plate was created for the suits which included an attachment ring similar to the one in the isolator and an inlet valve - *Figure 1*. A half-suit is suspended by the shoulder hooks above the inflation plate, and then attached to the plate with a standard half-suit

Figure 1. Inflation plate for half-suits. Note inlet valve on right with 'quick disconnect' connector.

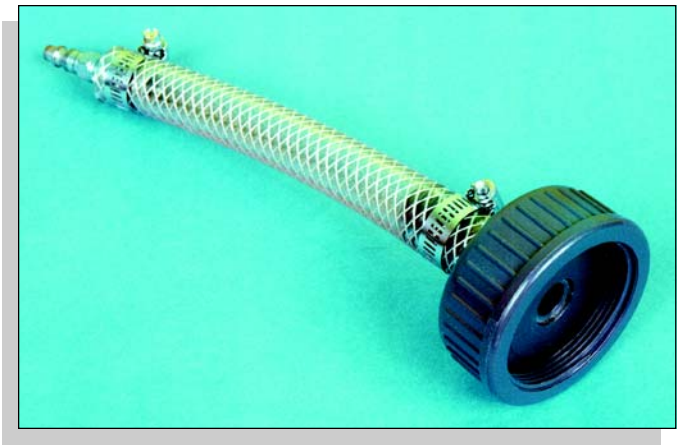

Figure 2. Air inlet connector for waste containers.

rubber band and clamp. Since leaks are frequently discovered near the base of the suit skirt, the suit should be clamped to the plate exposing as much of the skirt as possible. (In the isolator, the suit is slid to the bottom of the clamping ring before attaching the rubber band and clamping band. On the inflation plate, the suit is slid on, the rubber band attached, and the suit slid up to the top of the clamping ring before attaching the clamping band. An air hose connects the benchtop air inlet to the inflation plate (for ease of use, it is recommended to use 'quick disconnects' for all connections). The air valve on the benchtop is opened (30-40 psi, 2-3 kg/cm^2), and the valve opened on the inflation plate. The suit is fully inflated, but not overly stressed, and all valves are closed. This allows thorough visual inspection of the entire suit.

Originally, a pressure gauge was to be used to monitor pressure decay, but since the relative pressure inside the suit is quite small, the pressure was simply gauged by the height of the suit arms. Drooping arms indicated a leak in the suit.

It was discovered that inflating the suits made them easier to clean. Before using the inflation plate, the suits were cleaned by laying them across a table or hanging them by the shoulder hooks, and wiping them down with cloths. An inflated suit is much easier to clean and dry since folds and creases are minimized. Using a mild soap solution to wash the suits also can reveal leaks since holes in the suit will cause bubbles as the soap solution is passed over them.

Deflating the suit is achieved by simply unhooking the clamping band.

Waste Containers

An air inlet connector was created using a sterilization inlet cap and a short piece of pressure hose - *Figure 2*. This air inlet connector is attached to the sterilization inlet port of a clean, empty waste container. An air hose with 'quick disconnect' connectors is then used to attach the benchtop air inlet to the air inlet connector. The waste container is inflated, being careful not to overinflate. The fully extended waste container is now easy to visually inspect for holes.

The pressure decay in the waste container can be measured by watching the air inlet connector. If there is a hole in the container, the connector will droop.

To deflate the waste container, the air hose is disconnected from the air inlet connector.

Phase II: Ammonia Leak Testing

Although utilizing these inflation methods for visual leak testing greatly increased the chances of finding holes, there was still a desire to find a way to ammonia test the half-suits and waste containers. The first step in the process was modification of a pressure can. A small pressure can was obtained, and the dip tube was removed. The intent of this process is to transfer ammonium hydroxide vapor, not liquid. Next, 'quick disconnect' connections were added so the pressure can could be connected and disconnected easily from the hoses - *Figure 3*. A second air hose also is required, and it also should contain the 'quick disconnect' connections.

Ammonia Testing Half-Suits

The biggest concern with ammonia testing the suits was being able to exhaust the ammonia so an analyst could climb into the suit and hook it back into the isolator. An attempt was made to exhaust the ammonia through another valve in the base of the inflation plate, but the suit did not deflate very efficiently (this extra 'outlet' valve may be seen on the left side of the inflation plate in Figure 1). This problem was solved by cutting the fingers off a suit glove, and using a PVC pipe connector and hose clamps, attaching it to a piece of 2" (50 mm) general use 'flat' rubber hose - *Figure 4*. The other end of the rubber hose is attached to the isolator exhaust manifold via a valve.

Additionally, to ensure that the ammonia vapor circulated throughout the suit, a piece of tubing was attached to the inside of the inflation plate inlet. A 4-way tubing connector was used, allowing the insertion of one piece of tubing down the non-exhaust arm, one in the helmet, and one in the bottom of the inflation plate.

To ammonia test a half-suit, a suit was suspended from the shoulder hooks above the inflation plate. A small piece of yellow test cloth was tied to the inside framework of the helmet (so the color change can be observed). One of the ends of the circulating tubing was secured in the helmet (it was tied to the helmet framework with the yellow test cloth), a second piece of tubing was placed into the non-exhaust arm of the suit, and the third piece of tubing was allowed to dangle in the bottom of the inflation plate. The suit was attached to the inflation plate as stated above to allow maximum exposure of the skirt. The 'other' glove was removed from the suit, and replaced with the exhaust glove/tubing. The pressure can was placed into a fume hood and the lid removed. A small amount of fresh ammonium hydroxide (at room temperature) was poured into a small bottle. This container was placed into the pressure can, and the lid replaced. (It should be noted that originally the ammonium hydroxide was poured directly into the pressure can, but the resulting post-leak testing cleanup was difficult. Placing the liquid into a removable bottle made cleanup and disposal much easier.) One hose connected the benchtop air inlet to the inlet side of the pressure can. A second hose connected the outlet side of the pressure can to the inlet valve of the inflation plate. The exhaust manifold valve (where the glove/tubing is attached to the manifold) was opened. The benchtop air inlet and the inflation plate inlet were both opened. Air now circulated through the pressure can, past the ammonium hydroxide, and entered the suit. When the yellow test cloth began to turn green, the exhaust manifold valve was closed so the pressure could build up in the suit. When the suit was at the desired inflation, the inflation plate valve was closed (the benchtop air inlet valve would likewise have accomplished the same effect). The inflated suit is shown in Figure 4. The suit was washed with a mild soap solution, rinsed, and dried thoroughly. A yellow test cloth was used to inspect the suit for leaks, and

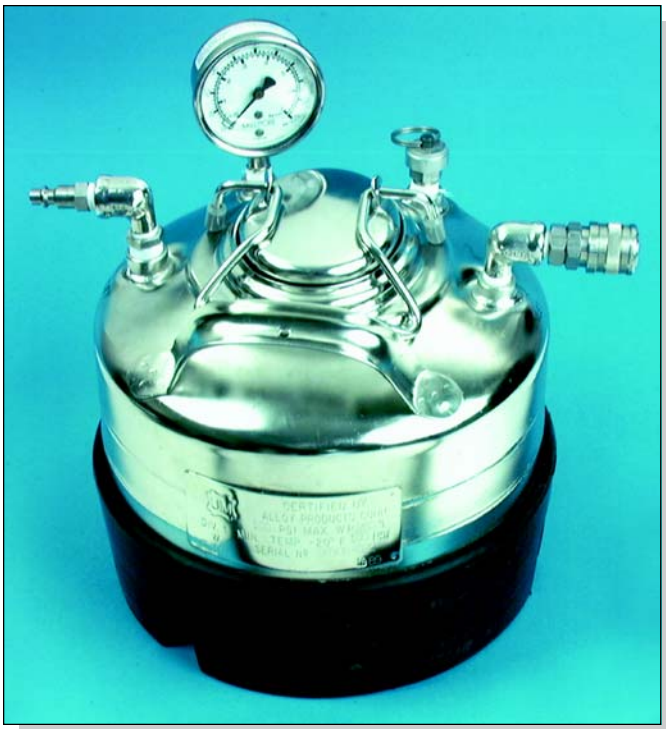

Figure 3. Pressure can with dip tube removed and 'quick disconnect' connections added.

holes were patched as necessary. (Patching a leak is performed easily with the suit inflated, as the pressure inside the suit exerts resistance against the patch; the small amount of air coming out of the hole usually does not interfere with the adhesion of the glue). Now, the ammonia vapor had to be cleared out of the suit. First, the exhaust manifold valve was opened to release the pressure from the suit. The benchtop air inlet valve was confirmed closed, and any residual pressure was relieved from the pressure can by using the pressure relief valve. The air line was disconnected from the benchtop inlet line, and the air line from the outlet of the pressure can was removed and attached to the benchtop air inlet. To contain any residual vapor, the free end of the air hose was attached to the outlet of the pressure can to make a closed loop. Now the benchtop air valve and the inflation plate inlet valve were opened, and the exhaust manifold valve was confirmed to still be open. The air flow was adjusted at the benchtop air inlet (the inflation plate valve would accomplish the same task) to keep the suit approximately halfway inflated, and air was allowed to purge the suit until the test cloth in the helmet changed from dark green to light yellow. When this occurred (approximately 30-60 minutes), the air inlet valve was closed and the suit was allowed to deflate. The exhaust manifold valve was closed, the glove/tubing was removed, and the suit glove was replaced. The half-suit was removed from the inflation plate, and the circulation tubing and the small piece of test cloth were removed. By holding the shoulder hooks, the suit was transferred to the isolator, and the suit was hung in the isolator (because of the residual ammonium hydroxide vapors, it is best not to enter the suit at this time). The half-suit air supply line was attached to the suit, and the air was turned on 100%. The air was permitted to circulate for at least 30 minutes before connecting the half-suit to the isolator attachment ring. By using this method, virtually no residual ammonia vapor has been found in the suit.

Figure 4. Inflated half-suit. Note the yellow test cloth in the helmet, and close-up of modified glove/exhaust line and close-up of 'high' clamping of the suit to the inflation plate.

Ammonia Testing Waste Containers

A clean waste container was obtained and connected to the sterilization outlet line. The sterilization outlet valve was opened. The air inlet connector was attached to the inlet of the waste container. The top plate of the waste container was removed, and a small piece of yellow test cloth was tied to the

Figure 5. Inflated waste container. Air inlet connector is on the left and the sterilization exhaust is on the right.

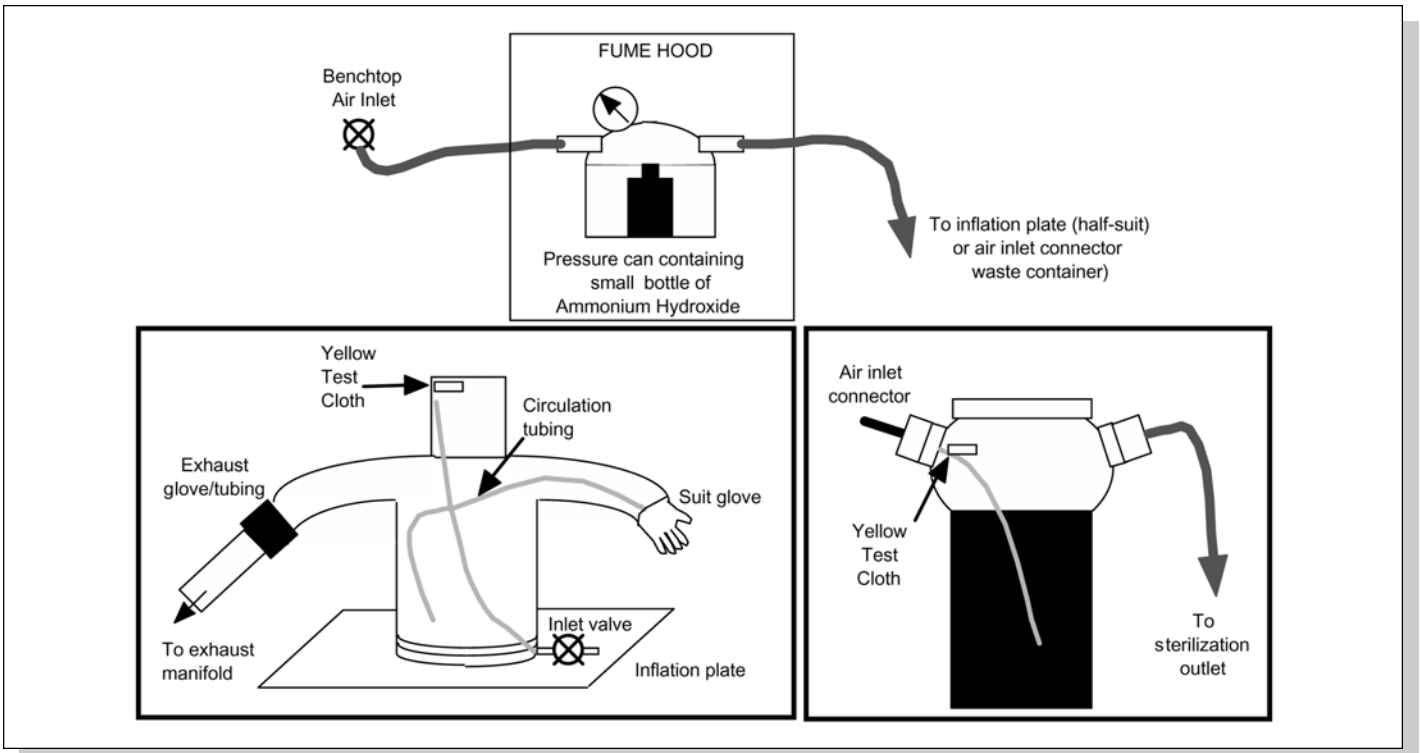

Figure 6. Overview of ammonia leak testing of half-suits and waste containers.

inlet tube near the top (so it could be seen through the plastic sleeve), and the plate replaced. The pressure can (with ammonium hydroxide and associated air lines) was prepared as mentioned above, and the air line from the outlet of the pressure can was attached to the waste container air inlet connector. The benchtop air inlet valve was opened, and when the test cloth inside the waste container began to turn green, the sterilization outlet valve was closed. When the waste container reached the desired inflation, the benchtop air inlet valve was closed. (Caution - the pressure can contains some residual pressure and will continue to inflate the waste container for a few seconds. It may be advantageous to close the air line before complete inflation, then adjust as needed later.) The inflated waste container is shown in Figure 5. A yellow test cloth was used to inspect the waste container for leaks, and holes were patched as necessary. Now, the ammonia vapor had to be cleared out of the waste container. First, the sterilization exhaust valve was opened to release the pressure from the waste container. The benchtop air inlet valve was confirmed closed, and any residual pressure was relieved from the pressure can by using the pressure relief valve. The air line was disconnected from the benchtop inlet line, and the air line from the outlet of the pressure can was removed and attached to the benchtop air inlet. To contain any residual vapor, the free end of the air hose was attached to the outlet of the pressure can to make a closed loop. Now the benchtop air valve was opened, and the sterilization outlet valve was confirmed to still be open. The air flow was adjusted at the benchtop to keep the waste container approximately halfway inflated, and air was allowed to purge the container until the test cloth in the sleeve changed from dark green to light yellow. When this occurred (approximately 30 minutes), the benchtop air inlet was closed and the waste container was allowed to deflate. The waste container lid was removed, the small piece of test cloth was removed, and the lid replaced. The sterilization outlet valve was closed, the inlet and outlet connections were removed from the waste container, and the waste container inlet and outlet caps replaced.

> ***The biggest concern with ammonia testing the suits was being able to exhaust the ammonia so an analyst could climb into the suit and hook it back into the isolator.***

Summary

Half-suits and waste containers are critical components of isolators, and thorough leak testing has not always been easily performed. This method of leak testing half-suits and waste containers is a relatively quick, efficient way to find holes. It only takes one hole to cause a sterility breach, easily justifying the extra effort to find and/or prevent it. See Figure 6 for the overview diagram.

About the Author

Thomas P. Burns is the Lead Scientist of the Sterility Laboratory for Eli Lilly and Company in Indianapolis, IN. In more than 15 years at Lilly, he has been involved with various areas of parenteral product testing, including the chemical and biological laboratories, technical services, and sterilization validation. Burns is a graduate of the University of Pittsburgh at Johnstown with a BS in chemistry. He can be contacted at 1-317/276-9207 or BURNS_THOMAS_P@Lilly.com.

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