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THE OFFICIAL TECHNICAL MAGAZINE OF ISPE

NOVEMBER/DECEMBER 2013 VOLUME 33, NUMBER 6

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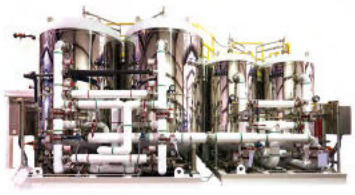

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Cleanliness and hygiene of facilities and equipment is a fundamental GMP expectation. The regulated company must ensure that residues of cleaning agents themselves do not affect patient and public safety. The acceptance criteria for residues and the choice of cleaning procedures and cleaning agents need to be defined and justified.

The articles in this issue demonstrate how companies are striving to achieve an effective approach based on scientific knowledge and appropriate risk assessment in all areas of regulated practices.

Walsh, et al, presents a comprehensive overview of current approaches to acceptance limits for cleaning agents. Some practical difficulties of application of these approaches are outlined in illuminating case studies. These suggest that these approaches err on the side of conservatism, and have been problematic for the industry. The authors propose an alternative science and risk-based approach based on that described in the ISPE Risk-MaPP Guide.

A similar science and risk-based approach is demonstrated in a case study by the ISPE Japan Affiliate, et al, that presents examples of risk evaluation method and case studies using Failure Mode and Effects Analysis (FMEA) to establish cost-effective countermeasures for cross-contamination in solid dosage form manufacturing facilities.

Contamination is also considered by Hanley-Onken and Cohen in their case study for the use of ozone to reduce the amount of biofilm contaminant in a pilot UPW production and delivery system.

Continuing the theme of science-based approaches, Dion and Parker explain how a good understanding of the basic scientific and engineering principles underlying steam sterilization can help with avoiding most common mistakes made when using steam autoclaves.

Combining scientific, regulatory, and technical aspects, but not overlooking the ever-increasing drive for cost-efficiency, Crone presents an economic case for the use of on-line Total Organic Carbon (TOC) and conductivity analysis for validating automated clean in place cycles.

Also covering economic, regulatory and technical considerations, and looking at another aspect of facilities and equipment, Masiello examines how cogeneration (the sequential generation of heat and power from a single fuel source) may bring operational, economic, and environmental benefits.

Hoffman, et al, similarly address power issues, but from the angle of consumption rather than generation, presenting a comparison of energy needs for ventilation and air conditioning systems with different RABS and isolator configurations.

Bohn explores some of the challenges and opportunities that can be encountered when bringing legacy facilities into compliance with current good manufacturing practices, and how effective validation master planning can facilitate the achievement of strategic objectives.

An article by Lipa, et al, reminds us that the knowledge of the organization is as much an asset as the physical plant and equipment, and illustrates through use of a case study, an example of the development of a knowledge management program and strategy.

I hope you find this issue of *Pharmaceutical Engineering* informative as well as thought provoking. I welcome your feedback – email me at ghall@ispe.org.

Gloria Hall
Editor, *Pharmaceutical Engineering*

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The Strength of the Past has Enabled a Strong Today and an Even Stronger Future

Berg discusses how the Society is positioned for growth in 2014 with the implementation of contemporary changes to some traditional approaches to product development and delivery, including the magazine, training, meetings, and conferences.

This is the time of year when many reflect on the year that is passing and begin to plan for the year ahead. This has been a very exciting year for ISPE Members as we continued to evolve the Society's relevance for a diverse global Membership. In 2013, Members led new initiatives and extended the Member experience locally through strong Affiliate and Chapter efforts and increased information-sharing via the ISPE Communities of Practice. This year, the ISPE International Board of Directors approved a new Business Plan as well as changes in program implementation for 2014 and the future looks very bright.

As ISPE turns the page on 2013, I would like to acknowledge the Members responsible for the Society's success, completion of many annual activities, and the planned transition of some long-standing programs. Members and Volunteers are the heart of ISPE—the reason the Society exists and prospers. Thank you to thousands of Members and their companies who have contributed to the Society's growth since ISPE was formed in 1982. ISPE has led many important activities over the years and while today's programs are front and center, we must never forget that the strength of the past enables a strong today—and a strong future. Thank you for your leadership—we look forward to your contributions in 2014 and beyond.

This year, we've changed *Pharmaceutical Engineering* Magazine to include a new editorial strategy with eight "departments" and lead articles on relevant hot topics. This new format provides Members with unique high quality technical information—the papers and articles appearing in our magazine are often the first or the only published document on a topic and available exclusively to ISPE Members.

In 2014, we plan to add more regulatory news to our publications and *Pharmaceutical Engineering* Magazine will feature articles and even some provocative interviews focused on regulatory issues. Further, we plan to keep those discussions alive through ISPEAK, ISPE's new blog that was just released (see http://blog.ispe.org/).

Through our Magazine, ISPEAK and other programs, ISPE Members have the opportunity to weigh in on discussions influencing how regulations and best practices are shaped and advanced. Interaction with Regulators has been a major theme for ISPE this year and their involvement is a true sign of the importance of ISPE and the value Regulators derive in interaction with all of you. This year, a record number of Regulators from more than 20 countries participated in our events; contributed to our documents and served as leaders and peer-contributors to our global Initiatives, such as Drug Shortages, Quality Metrics and many others.

There is an exciting year ahead of us. Your Society's goal to be a leading resource of timely information is the basis for the changes in our traditional magazine and I hope you are noticing similar changes in our training, meetings and conferences. In the next issue, I'll share more details on 2014 initiatives and events that you will not want to miss.

My very best to our Members, their families and companies for a prosperous New Year.

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Cleaning Validation for the 21st Century: Acceptance Limits for Cleaning Agents

by Andrew Walsh, MS, Mohammad Ovais, MP, Thomas Altmann, Gr FC, and Edward V. Sargent, PhD

This article presents currently suggested approaches to setting acceptance limits for cleaning agents, some of the difficulties with these approaches, emphasizing the need to move to a health-based approach as was suggested for APIs.

Two previous articles in this series discussed acceptance limits for Active Pharmaceutical ingredients (APIs) and moving to a health-based approach.[1-2] This article will discuss the currently suggested approaches to setting acceptance limits for cleaning agents, some of the difficulties with these approaches, and emphasize the need to move to a health-based approach as was suggested for APIs.

This discussion needs to begin with the origins of the FDA's expectations for cleaning validation regarding detergents as cleaning agents. The assumptions, rationale, and basis and even the thought processes resulting in requirements for setting acceptance limits for cleaning agents will be reviewed. As with the articles on APIs, we need to take a historical approach and go back to the FDA's:

Guide to Inspections: Validation of Cleaning Processes

The original guide[3] was conceived in 1992 by a number of inspectors in the MidAtlantic region during the Barr Laboratories case in part as a reaction to Judge Wolin's criticism of the GMPs for being vague and lacking detail. This Guide was intended to be very detailed and specific and was meant to clarify what their expectations were for cleaning validation.

The guide was updated and adopted for national use in 1993. Toward the end of the Guide under "Other Issues," there is a short section with concerns about detergents. In this section, the guide states:

> *"If a detergent or soap is used for cleaning, determine and consider the difficulty that may arise when attempting to test for residues. A common problem associated with detergent use is its composition. Many detergent suppliers will not provide specific composition, which makes it difficult for the user to evaluate residues. As with product residues, it is important and it is expected that the manufacturer evaluate the efficiency of the cleaning process for the removal of residues."*

The FDA made it clear that they expected companies to test for detergent residues not just API residues, which was a point of contention during the Barr Laboratories case. Judge Wolin agreed with FDA and stated that:

> *"...firms must identify the cleaning agents used in its (sic) cleaning processes. When these agents are known to cause residues, the company must check for the residue."*[4]

Then, after pointing out how difficult it is for companies to

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evaluate detergent residues, the FDA went on to state:

> *"However, unlike product residues, it is expected that* ***no**** *(or for ultra sensitive analytical test methods –* ***very low****) detergent levels remain after cleaning."*

The FDA had just acknowledged how difficult it was to test for detergent residues and then required that companies demonstrate that no residues (or at least very low) are present. This follow-up statement was, in effect, a "Catch 22" for companies and put them into a difficult situation; most companies at that time had no analytical methods available for detergents and these can be difficult to develop.

And if testing for detergent residues wasn't enough of a challenge, the guide goes one step further and states:

> *"Detergents are not part of the manufacturing process and are only added to facilitate cleaning during the cleaning process."*

This last statement created some confusion. Clearly, the API in Product A is not part of the manufacturing process for Product B, yet the FDA accepts that there can be residues of the API for Product A in the manufacturing equipment during the manufacture of Product B. Why did they not expect "no (or for ultra sensitive analytical test methods – very low)" levels for API residues then? It would seem that drug residues are less of a concern than detergent residues which begs the question: Are detergents really that unsafe?

On the other hand, the regulations (21 CFR 211.67(a)) clearly state that:

> *"Equipment and utensils shall be cleaned,..."*

If this is so, cleaning is a required operation in manufacturing. Cleaning involves the use of cleaning agents (detergents or surfactants). So if the regulations require cleaning and cleaning involves cleaning agents, clearly cleaning agents are a required part of the manufacturing process.

These issues with using detergents also affected the...

Determination of Acceptance Limits for Cleaning Agents

As with APIs, acceptance limits for cleaning agents need to be established to evaluate any swab or rinse samples taken for residues of these cleaning agents. Unlike APIs, where limits have been set based on a fraction of the APIs lowest therapeutic dose, cleaning agents have no therapeutic dose in humans so this approach could not be used.

The Hall Approach

An alternative approach was first proposed by Dr. William Hall in 1999 in an article[5] and is described in more detail in the book "Pharmaceutical Process Validation."[6] This approach was adopted in a modified form by the Parenteral Drug Association in 1999[7] and in a greatly simplified form by CEFIC/APIC also in 1999.[8]

The approach presented by Dr. Hall is:

First, $NOEL = LD_{50} \times 0.0005$

Where: NOEL = No Observable Effect Level
LD_{50} = Lethal Dose required to kill 50% of the test population
0.0005 = "a constant derived from a large toxicology database"*
*(Definition used in Dr. Hall's article)

Second, $ADI = NOEL/SF$

Where: ADI = Acceptable Daily Intake
SF = Safety Factor

So the conversion from acute LD_{50} to an ADI depends on two aspects:

1. Conversion from acute LD_{50} to $NOEL_{chronic}$ by multiplying by 0.0005 (or dividing by 2000) commonly known as the "empirical factor", and
2. Derivation of an ADI value by inclusion of a "route of administration"-based Safety Factor.

The examples in Dr. Hall's article use 100 as a Safety Factor for a product administered by the oral route and 5,000 for a product administered by the intravenous route, but no specific references for the origin of these values was provided. These calculated ADI values are then used in the typical cleaning validation equations for calculating a Maximum Allowable Carryover (MAC or MACO).[1,2]

The combination of the factors used in the two calculations comes to a total factor of 200,000 and 10,000,000 for the oral and intravenous examples respectively to convert from an LD_{50} to an ADI.

Hall states that his approach is based on ideas described in a series of papers published by the Environmental Protection Agency,[9] the Army Bioengineering Research and Development Laboratories,[10] and the Toxicology Department at Abbott Laboratories.[11] Let's examine these papers.

The Dourson and Stara Article

Dourson and Stara[9] published an important review of the origins of safety factors (referred to as uncertainty factors in their article) used for risk assessment.

For the use of uncertainty in the derivation of Acceptable Daily Intakes (ADIs), Dourson and Stara provide the following calculation:

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10	Used when extrapolating from valid experimental results from studies on long term ingestion by man (this 10 fold factor protects the sensitive members of the human population estimated from data garnered on average healthy individuals).
100	Used when extrapolating from valid results of long term feeding studies on experimental animals with results of studies of human ingestion unavailable or scanty (this represents and additional 10-fold uncertainty factor in extrapolating from the average animal to the average human).
1,000	Used when extrapolating from less than chronic results on experimental animals with no useful long term or acute human data (this represents and additional 10-fold uncertainty factor in extrapolating from less than chronic to chronic exposures).

Table A. Uncertainty factors for converting no effect levels to ADIs.

$$\text{ADI} = \frac{\text{“no effect” level}}{\text{uncertainty factor}}$$

The review discusses an article by Lehman and Fitzhugh of the FDA[12] dating back to 1954 that suggested calculating an ADI by dividing an NOEL or NOAEL (No Observable Adverse Effect Level) by 100. The rationale being that a factor of 100 accounted for uncertainties in differences between animals, variations in sensitivities, size of test populations, etc. They go on to say that the FDA then later recommended an uncertainty factor of 1,000 when only data from sub-chronic studies were available and 2,000 when the data was available from only one species. The authors reviewed the literature and show that uncertainty factors of 10, 100 and 1,000 are suggested when extrapolating an ADI from data under different circumstances. The guidelines provided in their article are shown in Table A.

Basically, the uncertainty factor of 1,000 is derived from a factor of 10 for intraspecies differences, a factor of 10 for Interspecies differences, and a factor of 10 for adjustment from sub-chronic to chronic exposure.

The authors then provide an analysis of intraspecies adjustments, interspecies adjustments and chronic and sub-chronic exposure adjustments to show that each factor of 10 is conservative and that factors of 3 to 5 are sufficient in most cases. They also give an example where an uncertainty factor of 1,000 may be overstated by a multiple of 5 and an uncertainty factor of 200 may be more appropriate.[9]

In summary, Dourson and Stara's article indicates factors from 10 to 1,000 to convert from a “no effect” level to an ADI.

The second paper from the Army Bioengineering Research and Development Laboratories has become known in the Cleaning Validation community as:

The Layton Article

Layton, et. al.,[10] in their article were concerned with estimating Acceptable Daily Intakes (ADIs) of potentially toxic substances encountered at hazardous waste sites. Most chemicals have no human toxicological or chronic toxicity data and this makes it very difficult to determine the health risks due to exposure to such environmental contaminants. Consequently, the authors attempt to derive a method to convert acute animal toxicity data (i.e., LD_{50} values) to human ADIs. This was done by evaluating a database of compounds with known LD_{50}s and NOELs and selecting a conversion factor that corresponded to the 5th cumulative percentile, that is, 95% of the conversion factors from the database were lower. The authors warn that:

> *“This paper focuses specifically on the use of oral LD_{50}s to provide **provisional*** estimates of the acceptable intakes of noncarcinogenic chemicals. These estimates are meant to be conservative; that is, if the ADI could be computed from a NOEL determined in a chronic toxicity study, it would nearly always be higher than the value estimated from the LD_{50}.”*
>
> *(Emphasis from the original article)

Layton, et. al., make it clear that the approach in the article may be appropriate for compounds that have very little to no toxicological data available and clearly note that if additional data were used, any calculated ADI would almost inevitably be higher.

A large database of pesticides was used for the evaluation and they note that pesticide studies look at cholinesterase inhibition which typically generate lower ADIs than other toxic effects. After reviewing the database they write:

> *“We suggest values from 5×10^{-6} to 1×10^{-5} day^{-1} for establishing interim ADIs from oral LD_{50} data (in mg kg^{-1}). The use of such factors is meant primarily for situations where there is a need to manage the health risk of exposures to contaminated soils, waters, crops, or other material at a particular site.”*

However, in their conclusion, the authors make note that:

> *“We recognize, though, that in some instances it might be desirable to use higher or lower conversion factors. The NOEL/LD_{50} ratios given in this paper can easily be reevaluated to establish different conversion factors.”*

In summary, the Layton article indicates factors from 200,000 to 100,000 to convert from an LD_{50} to a *provisional* ADI, while recognizing that these factors were based

Patient Exposure	Dosage	Safety Factor
Short Term Use	LD_{50} animal	>100
Prolonged Use	LD_{50} animal	≥ 1,000
Lifetime Use	LD_{50} animal	≥ 1,000

Table B. Factors for converting LD50s to ADIs from Conine, et. al.

in part on a very conservative endpoint (cholinesterase inhibition) and that the ADI would be higher (i.e., lower Safety Factors used) with additional information.

The Conine Article

The third paper by Conine, et. al.,[11] developed a method for establishing residue limits specifically for pharmaceutical products and medical devices. In particular, this article addressed the different exposures that a patient may experience with products that are administered over a lifetime or on a long term basis (e.g., daily injections of Insulin) vs. products that are administered on a one time or short term basis (e.g., an emergency use of Epinephrine). It seems obvious that limits in these very different circumstances should be different.

These authors proposed that limits be derived for three different categories: for short-term use, for prolonged use, and for lifetime use. Correspondingly, acute data should be used to set short-term limits, subchronic and reproductive effects data should be used for prolonged exposure limits and chronic/lifetime data should be used for lifetime limits. The authors emphasized the importance of using high quality data and that regardless of the limit being set (short-term, prolonged or lifetime) that ***all data should be taken into consideration***. Table B summarizes the factors suggested for converting LD_{50} data into an ADI.

The authors added a footnote to all their tables that acknowledged:

> *"The actual factor may be modified on the basis of the data under evaluation and **the professional judgment of the toxicologist performing the evaluation*** to arrive at the actual safety margin to be applied. In each case an additional modifying factor between 1 and 10 may be applied. In addition, since acute data represent the least acceptable data for calculation of acceptable daily intake values for lifetime exposure, the range of modifying factors based solely upon such data may be expanded."*
>
> *(Emphasis added)

They then provide the following calculation:

$$\text{ADI (mg/day)} = \frac{\text{NOEL, LOEL, etc. (mg/kg/day)} \times \text{human body weight (kg)}}{\text{safety margin}}$$

Where: safety margin = safety factor × modifying factor

In summary, the Conine article indicates factors from 100 to 1,000 to convert from an LD_{50} to an ADI with an additional modifying factor between 1 and 10 in most cases, or possibly more, depending on the data used.

After reviewing the content of the articles by Dourson and Stara, Layton, et. al., and Conine, et. al., it is difficult to determine exactly how Dr. Hall used these references since the authors cannot find any connection between the safety factors proposed by these articles and the ones proposed by Dr. Hall. For example, the origin of the safety factor of 5,000 used to calculate the ADI from the "No Observed Effect Level" in the intravenous example is not found in any of these articles. An important observation to make is that, while the authors of the articles warn that their approaches are very conservative and the Safety Factors should be probably lower in most cases, Dr. Hall chose to use even higher Safety Factors.

The Kramer Article

Another paper by Kramer, et. al.,[13] reviewed conversion factors used to convert short-term toxicity data (LD_{50}s) into NOAELs. Like the Layton article, this article looked at a database of compounds with known LD_{50}s and NOAELs and selected a conversion factor that corresponded to the 95% used by Layton, et. al., but also added in an upper 95% Confidence Interval to adjust for estimation errors in the analysis. In effect, this step makes the results of this approach 95% confident that the Conversion Factor is higher than 95% of the other compounds.

Like the Layton article, Kramer, et. al., points out that these types of approach may be inaccurate:

> *"The (Geometric Mean) of the ratios is the factor that converts a toxicity parameter into the most likely NOAELchronic. This factor may be **highly inaccurate for individual compounds*** because of the large variation between compounds."*
>
> *(Emphasis added)

Also like the Layton article, Kramer, et. al., point out that pesticides made up the majority of the database used in the analysis (approx 50%), followed by solvents (approx 25%) plus some metal containing compounds, phthalates and some other compounds.

This certainly biased the analysis on the high side leading to high values for the conversion factors. For example, the authors point out that the cholinesterase inhibitors as a subgroup of the database has a significantly lower Geometric Mean:

> *"Examination of the $LD_{50}/NOAEL_{chronic}$ ratio of the cholinesterase inhibitors resulted in GM = 197 and GSD*

= 5.8 (n = 28). The GSD was statistically significantly reduced (P < 0.05) compared to the GSD of complete data set…"

Since the cholinesterase inhibitors were included in the overall analysis, the values calculated by Kramer, et. al., are even higher and even more excessively conservative than for Layton, et. al.

While Dr. Hall did not reference the Kramer article, another author, Destin LeBlanc, uses values of 105 and 106 in several of his articles on cleaning agent limits[14-17] and does reference the Kramer article; but he references those of Layton and Conine as well, so it is not clear how they were derived as these values do not match the safety factors from any of the three articles. LeBlanc clearly believes that safety factors should be this high for cleaning agents as in Slide 18 of his 2008 webinar "Are we Setting Limits Correctly?"[17] LeBlanc states that concerning detergents:

"Conversion Factors like 5 × 10^4 are not appropriate; should be 10^5 or 10^6"

What should be clear is that LeBlanc suggests safety factors that are even more conservative than the safety factors found in these articles which their authors admit are overly conservative. A comparison of all these approaches with their point of departures and safety factors used can be seen in Table C.

Source	Dosage Used	Safety Factor
Lehman and Fitzhugh	NOEL or NOAEL	100
Dourson and Stara	"no effect" level	1,000
Layton, et.al.	LD_{50} animal	100,000 to 200,000
Conine, et.al.	LD_{50} animal	>100 (Short Term)
		≥ 1,000 (Prolonged)
		≥ 1,000 (Lifetime)
Kramer, et.al.	LD_{50} animal	1,700,000*
Dr. Hall's approach	LD_{50} animal	200,000 (oral)
		10,000,000 (intravenous)
LeBlanc approach	LD_{50} animal	100,000 to 1,000,000
*Kramer, et. al. indicated a Conversion Factor of 1.7 × 10^4 for an LD_{50} to an NOAEL with a most likely additional factor of 100 to convert to an ADI.		

Table C. Factors suggested for converting no effect levels/LD_{50}s to ADIs.

Industry and Regulatory Guidance

There have been a number of examples of industry guidance documents implementing some form of the toxicology-based approach proposed by Dr. Hall. In 2000, the CEFIC/APIC Guide[18] was greatly updated and presented the following approach:

$$NOEL = \frac{LD_{50}\ (g/kg) \times 70\ (kg\ a\ person)}{2000}$$

From the NOEL number a MACO can then be calculated according to:

$$MACO = \frac{NOEL \times MBS}{SF \times TDD_{next}}$$

Where: MACO = Maximum Allowable Carryover: acceptable transferred amount from the investigated product ("previous")
NOEL = No Observed Effect Level
LD_{50} = Lethal Dose 50 in g/kg animal. The identification of the animal (mouse, rat etc.) and the way of entry (IV, oral etc.) is important.
70 kg = 70 kg is the weight of an average adult
2000 = 2000 is an empirical constant
TDD_{next} = Largest normal daily dose for the next product
MBS = Minimum batch size for the next product(s) (where MACO can end up)
SF = Safety factor

The CEFIC/APIC Guide states that Safety Factor (SF) varies depending on the route of administration" with a factor of 200 for APIs that will be in oral dosage forms. CEFIC/APIC goes on to say that the SF can vary depending on substance/dosage form and lists ranges similar to those listed in PDA's Guide for Therapeutic dose calculations (Topicals: 10-100, Oral products: 100-1000, Parenterals: 1,000-10,000). This leaves the selection of Safety Factors up to the person doing the calculation which is usually the person writing the Cleaning Validation Protocol, but values anywhere from 20,000 to 20,000,000 are possible.

The implementation in the 1999 PDA Technical Report 29[19] was also slightly modified from the Hall approach and shows the following equations:

$$NOEL = LD_{50} \times \text{Emperical (sic) Factor}$$

and

$$ADI = NOEL \times AAW \times SF$$

where: NOEL = No Observed Effect Level
LD_{50} = Lethal Dose for 50% of animal population in study

empirical factor = " derived from animal model developed by Layton, et. al.
ADI = Acceptable Daily Intake
AAW = Average Adult Weight
SF = Safety Factor

The PDA equation did not specify a value for the "empirical factor" and instead refers to an "animal model" from an article by Layton, et. al.,[9] The ADI calculation is further modified to convert to a total dose rather than leaving the ADI in a mg/kg (or µg/kg) form. Although Hall states he used an AAW of 70 kg in his examples, he did not show it in his equations. This again leaves the selection of Safety Factors up to the person doing the calculation.

The PDA recently updated this Technical Report 29[20] and now suggests using the ISPE Risk-MaPP approach which requires a *qualified toxicologist* to determine the Acceptable Daily Exposure (ADE) based on all of the available clinical and toxicological data. However, the updated guide also offers as an alternative the following equation:

$$NOEL = \frac{LD_{50} \times BW}{MF_1}$$

where: NOEL = No Observed Effect Level
LD_{50} = the 50% Lethal Dose of the target residue in an animal, typically in mg/kg of body weight (by the appropriate route of administration)
MF_1 = modifying factor or factors, selected by the toxicologist

The cumulative modifying factors selected are generally no more than 1000. Once the NOEL is estimated, the SDI is determined by:

$$SDI = \frac{NOEL}{MF_2}$$

where: SDI = Safe Daily Intake of the residue
MF_2 = modifying factor or factors, selected by the toxicologist

The cumulative modifying factors selected are generally no more than 1000. Once the SDI is established the ARL is determined:

$$ARL = \frac{SDI}{LDD}$$

where: ARL = acceptable residue level in the next drug product
LDD = largest daily dose of the next drug product to be manufactured in the same equipment

This suggested approach also can lead to a combined safety factor of 1,000,000 which most workers would probably default to and avoid using a qualified toxicologist and sidestep the calculation of an ADE.

The PDA has also issued another guide on cleaning validation for biologics.[21] In this guide, "15.0 Appendix Carryover Calculations" provides an example calculation "based on the toxicity of a *cleaning agent for formulation/fill* manufacturing." Although the guide does not provide an equation per se, based on the example calculation provided it can be seen that the equation would be:

$$ADI = \frac{LD_{50} \times BW}{CF}$$

where: LD_{50} = Lethal Dose for Cleaning Agent
BW = Body Weight of patient taking product B
CF = Conversion Factor

The example goes on to state that the Body Weight used is 60 kg and the Conversion factor is 100,000.

Interestingly, when Health Canada released their Cleaning Validation Guidelines[22] in June of 2000 Section 10.0 "Establishment of Limits" they make no mention of a toxicological approach to setting limits but at the very end added the following note:

> *"Environmental Protection Agency and toxicologists suggest that an acceptable level of a toxic material may be that which is no more than 1/1000 of a toxic dose or 1/100 - 1/1000 of an amount which is not known to show any harmful biological effect in the most sensitive animal system known, e.g., no effect."*

Unfortunately there were no references provided and this passage does not exist on their current website. Health Canada opened their guide to comments in 2012 and currently does not provide the document on their website. Other guidelines such as the PIC/S Guidelines[23] and the WHO Guidelines[24] make no mention of calculating limits based on toxicological data at all.

Relevance of Currently Used Safety/ Conversion Factors

Overall, the pharmaceutical industry has had great difficulties with using the safety factors as suggested by Dr. Hall and LeBlanc. The following are three brief vignettes to underline the difficulties the use of these safety factors has created.

Case Study 1

A pharmaceutical company created a new cleaning validation standard and decided that the safety factor for their

Compound	LD_{50} (mg/kg^{-1})	NOEL ($mg/kg/day^{-1}$)	Factor to Convert LD_{50} to True NOEL
Benzalkonium chloride	400	94	4
Sodium dodecylbenzenesulfonate	1260	150	8
Tergitol 08	5750	290	14
Calcium disodium edetate	7000	375	18

Table D. Factors to convert LD_{50} to true NOEL (data from Layton, et.al.)

cleaning agents was inadequate and should be set higher. The safety factor they decided upon was 10^6 or 1/1,000,000 of the toxic dose (LD_{50}). Immediately, there was an issue with a cleaning agent used to clean one of their products. The new acceptance limits were now below the Method's LOQ and far below the rinse data that was being achieved during the cleaning validation for this product.

What was this cleaning agent? ***Isopropyl alcohol.*** However, Isopropyl alcohol is rated by ICH as a Class 3 solvent with low toxic potential and allowed in pharmaceutical products at levels up to 0.5%. The HERA Report[25] for Isopropyl Alcohol points out that "A substantial amount of toxicological data and information in vivo and in vitro demonstrates that IPA has a low order of acute toxicity." So why should the pharma industry need to apply such low limits for Isopropyl alcohol?

Case Study 2

Another pharmaceutical company was using a parts washer to clean equipment from a packaging line. Limits were calculated using 1/1,000,000 of the toxic dose (LD_{50}) and were below the limits of detection for the method. This company saw that it had two options: convert to disposable parts or stop using the cleaning agent. The company decided to stop using the cleaning agent and to wash with water only.

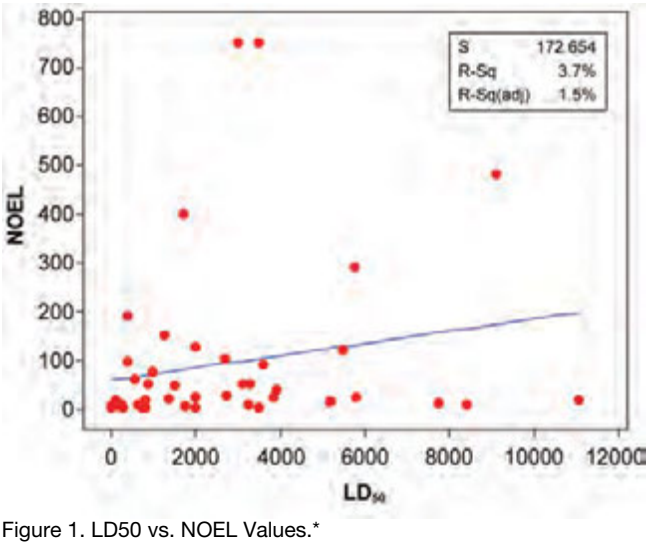

Figure 1. LD50 vs. NOEL Values.*

What was this cleaning agent? ***Sodium Lauryl Sulfate (SLS).*** However, SLS has a long history of use as a pharmaceutical excipient and as a food additive and is a common ingredient in toothpaste used by millions of people everyday. SLS is listed on the Inactive Ingredient Database and can be up to 40% in topicals and in tablets. Sodium Lauryl Sulfate is also on the EAFUS list of substances that the FDA has either approved as food additives or listed or affirmed as GRAS. EPA also has posted on its website "Sodium Lauryl Sulfate; Exemption From the Requirement of a Tolerance"26 that specifically exempts SLS from needing a limit for food. In addition, the FDA already allows SLS to be added to foods up to 1,000 parts per million.[27] Finally, the Organization for Economic Cooperation and Development Screening Information Data Set (OECD SIDS) concluded that "..sodium dodecyl (lauryl) sulfate is of no concern with respect to human health."[28] So why should the pharma industry need to apply such low limits for sodium lauryl sulfate?

Case Study 3

Another pharmaceutical company was manufacturing an injectable product. The Cleaning Validation Acceptance Limit for one of the cleaning agents used in cleaning this product was calculated to be < 10 ppb and could not be met.

What was this cleaning agent? ***Sodium Hydroxide.*** However, NaOH is a common component in the formulation of injectable drug products and in one product has been approved by FDA at 19.27%.[29] NAOH is not considered by the FDA to be unsafe and is on the Generally Recognized as Safe[30] (GRAS) lists and allowed as a food additive. It can be used "quantum satis" in Europe, meaning you can add as much as you need to achieve a specific effect (but not more than that). A common use for Sodium Hydroxide is pretzel manufacturing; the pretzel dough is formed and immersed into a 2-4% NaOH solution before the baking process. This procedure results in the typical brown and smooth pretzel surface.[31] So why should the pharma industry need to apply such low limits for Sodium Hydroxide? (Note: the ECHA review[32] concluded that no valid oral LD_{50} exists for sodium hydroxide. This greatly undermines the argument that the LD_{50} divided by some safety factor is valid for establishing cleaning limits).

At first consideration, it would seem that the recommended safety/conversion factors may be overinflated. Let's look at a few compounds where the LD_{50}s and the NOELs have been determined experimentally. Table D lists a few well known compounds listed in the Layton article that happen

to be used as cleaning agents. As can be seen, the factor needed to convert their LD_{50}s to their true NOEL are much less than the 1,000 to 2,000 suggested by the above articles and guidance. For Benzalkonium chloride, the conversion factor is only 4 which is 500 times lower that those suggested. So the initial assumption of 2,000 is clearly too high in these cases.

Compound	LD_{50} – Rat (mg/kg)	Hall ADI (mg/day)	LeBlanc ADI (mg/day)	Risk-MaPP ADE (mg/day)
Isopropyl alcohol	4710	0.024	0.0047	50
Sodium lauryl sulfate	1288	0.006	0.0013	10
Sodium dodecylbenzene sulfonate	1260	0.006	0.0013	63
NaOH	4090	0.02	0.0041	20

Table E. Comparison of the Hall, LeBlanc, and full toxicological evaluation (ADE) approaches.

Let's examine the relationship between the LD_{50} and the NOEL. Figure 1 shows a plot of LD_{50}s and their known NOELs from the Layton article which shows a clear lack of linearity (R^2 = 1.5%). This clearly indicates that using a single factor to convert all LD_{50}s to their equivalent NOELs will be highly inaccurate.

To examine if the limits derived through the Dr. Hall and Leblanc approaches are overly conservative, ADIs were calculated for the three cleaning agents discussed in the case studies (plus one additional) using both approaches and the results compared to ADEs determined by a highly trained and experienced toxicologist using the approach described in the ISPE Risk-MaPP Guide that considers all the available data on the compounds. The results can be seen in Table E.

The results obtained by the Dr. Hall and LeBlanc approaches are not only different from the ADE calculated by a qualified toxicologist, they are almost 10,000 times lower. These results clearly demonstrate that approaches that only use a conversion factor with an LD_{50} result in excessively conservative limits and that the ADE approach of Risk-MaPP, which considers all available data, results in far less restrictive limits. These results also explain the obvious disconnect between the limits using the Hall and LeBlanc approaches and the well-known innocuous nature of these compounds. In many cases, the approaches used in the industry today for calculating limits for cleaning agents are a case of severe overkill.

Where Does the Industry Go From Here?

As discussed previously, the Layton article pointed out that ADIs calculated using the factors they presented (5×10^{-6} to 1×10^{-5} day^{-1}) should be considered *provisional*; Kramer, et. al., acknowledge that their approach may be *highly inaccurate for individual compounds*, and Conine, et. al., emphasize that *all data should be considered* in setting an ADI and not just LD_{50}s. As was pointed out above that guidelines involving chemicals no longer require LD_{50}s to be determined and toxicologists no longer derive them.[33] So, in the very near future, LD_{50}s will no longer be available and these calculations cannot be applied. The authors hope that readers would agree that simply using safety/conversion factors with LD_{50}s is too inaccurate and too conservative for use in setting limits for cleaning agents and that a qualified toxicologist should be used for this task. Using the approach described in the ISPE Risk-MaPP Guide, a qualified toxicologist can evaluate all the available data and determine an Acceptable Daily Exposure (ADE) for use in calculating Maximum Safe Carryover (MSC) limits for cleaning agents. The setting of limits also should not be restricted just to patient safety, but also to product quality and this should be part of the hazard identification step in a risk assessment. Subsequently, after cleaning data has been collected, Statistical Process Control (SPC) limits can be calculated for cleaning agents as described in the previous articles.[1-2]

Another point to consider is that the FDA expects limits to be scientifically justified. The FDA's guide specifically states this. In Section V. Establishments of Limits, the last sentence reads:

> *"The objective of the inspection is to ensure that the basis for any limits is scientifically justifiable."*

Clearly, there is not a strong scientific case for using conversion/safety factors from the sources that have been cited as they lead to grossly inaccurate and excessively low values. Having a qualified toxicologist evaluate all the available data and determine an acceptable daily exposure provides a scientifically justifiable approach.

Also as mentioned above, one reaction of the industry to these unachievable limits has been to avoid using detergents and cleaning agents altogether. There are many companies that are now arguing that since their API is water-soluble, then water is all they need to clean their equipment. Eliminating detergents from the cleaning process is actually a dangerous practice. Cleaning with water only, or with very low amounts of cleaning agents, can allow residues to build up over time in crevices and hard to reach areas (consider bathing for a month without soap or shampoo). This practice also has been associated with the occurrence of unknown (extraneous) peaks in cleaning validation HPLC samples.[34] Hopefully, using the ADE approach will develop more accurate and more reasonable limits which should enable companies to use cleaning agents freely and without concern. The development of ADEs of cleaning agents also should provide more assur-

ance to regulators about the relative safety of cleaning agents and encourage the return to their use in cleaning.

Summary

This article's brief review the origins of the safety/conversion factors used in the toxicology arena have shown these approaches to err deeply on the side of conservatism. The implementation of these approaches for setting acceptance limits for cleaning agents have likewise been overly conservative and have been problematic for the industry. It should be clear that an evaluation of a cleaning agent by a qualified toxicologist or pharmacologist, *considering all the available data,* to select conversion/safety factors (where appropriate) will provide legitimate and much more workable limits for cleaning agents for use in cleaning procedures. Table F below compares the two approaches.

This article should not be viewed as just a simple condemnation of current practices in the industry concerning setting limits for cleaning agents. Attempts were made in the past to provide an industry struggling with setting limits for cleaning agents with something to work with. However, without such a critical review, the industry cannot break from past practices, change, and move forward.

These changes in view and approach will hopefully free the pharmaceutical industry to return to using many common cleaning agents without undue concern and encourage the industry to truly clean their pharmaceutical manufacturing equipment. The appropriate use of cleaning agents should not be hindered by unnecessarily conservative limits and should allow for effective and complete removal of process residues, and in so doing, provide a higher degree of safety to the patient. The appropriate use of cleaning agents also can allow shortened cleaning times, reduced water usage, increased operator safety and improved operational efficiencies for the pharmaceutical industry.

LD_{50} Approach	ADE (Risk-MaPP) Approach
Uses LD_{50} values alone as indicator of patient health hazards *(provisional approach became first-line approach for estimation of limits)*	Holistic approach! Uses all the toxicological / pharmacological data to identify, assess and characterize risks that are relevant to patient exposure
LD_{50} determinations have been discontinued	ADE or Permitted Daily Exposure (EMA Term) are the current approach
Limit calculations based on LD_{50} can be performed by unqualified personnel	ADEs determined by Qualified Pharmacologist / Toxicologist
Safety factors are based on route of administration and not on the actual risk posed by the residue	Uses data-derived safety factors (where needed) in the estimation of acceptable (safe) exposure
Uses literature-based conversion factors to derive ADIs	Uses data to derive ADEs
Cannot be used for deriving limits for cleaning agents with limited data (e.g. when no valid LD_{50} value is available).	ADEs can be established for cleaning agents with limited data (e.g. by using approach based on Threshold of Toxicological Concern concept).
May not be applicable to routes for which LD_{50} values are not available	Route-to-route extrapolation possible. Can be used to characterize all the potential exposures
Derived Limits are overly conservative and often impractical, unachievable and unverifiable	Derived Limits are realistic and practical, achievable and verifiable and ***safe***

Table F. Comparison of two cleaning approaches.

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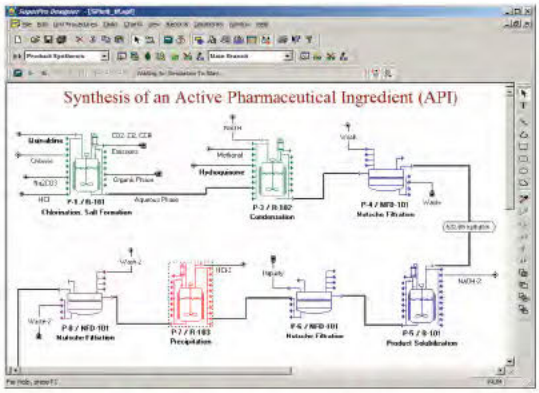

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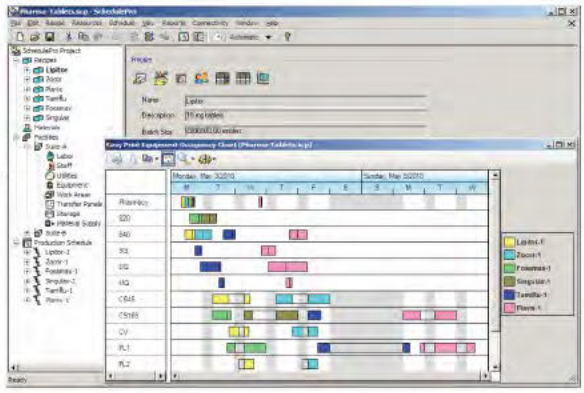

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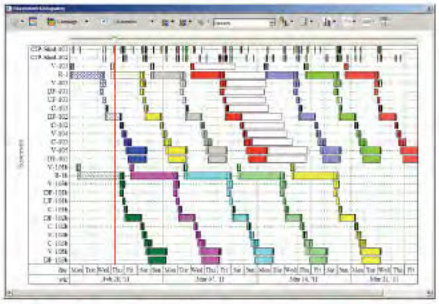

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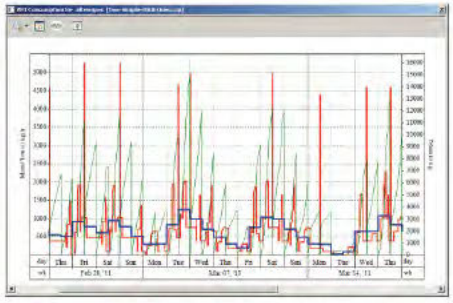

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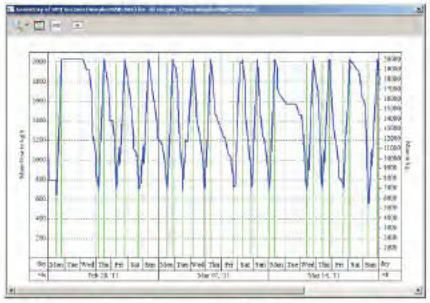

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Risk Assessment for Cross-Contamination in Solid Dosage Form Manufacturing Facilities

by Mock FMEA Special Interest Group (SIG), Containment COP, and ISPE Japan Affiliate

This article presents a risk evaluation method and case studies using Failure Mode and Effects Analysis (FMEA) introduced in ICH Q9 to establish cost-effective countermeasures for cross-contamination in solid dosage form manufacturing facilities.

ISPE developed a Baseline® Guide, Risk-Based Manufacture of Pharmaceutical Products (Risk-MaPP),[1] using a scientific risk-based approach to maintain product quality and worker safety in order to reflect the importance of quality risk management as defined by ICH Q9.[2] Professionals with varied experience representing a number of pharmaceutical companies in the US, EU and Japan collaborated on the development of the Risk-MaPP Guide. The content of the Guide was reviewed by the US Food and Drug Administration (FDA) and acknowledged in the forward section of the guide.

The Containment Community of Practice (COP) of ISPE Japan Affiliate has been committed to the development and the implementation of Risk-MaPP from the beginning.

In this article, some examples of the risk assessment based on Risk-MaPP are provided for the prevention of cross-contamination in solid dosage form manufacturing facilities and summarized in the Appendices.

The four routes of cross-contamination indicated in Risk-MaPP are listed below in order of importance:

- Mix-Up: mix-up of API, process, potency, labeling, etc.
- Retention: carry over on product contact parts, failure to clean to limits of product to another product on gowning and equipment
- Airborne Transfer[3]: sedimentation of aerosols from one product into another

When executing a risk assessment, it may be reasonable to leave issues related to mix-up and retention to the existing GMP and cleaning validation activities since GMP guidelines provide recommendations for prevention of cross-contamination. In most existing manufacturing, countermeasures for cross-contamination attributed to mechanical and airborne transfers have been based on visual inspection on non-product contact surfaces, such as containers, floors, walls, corridors and fittings. When highly potent products (as opposed to general products) are manufactured, judging by visual inspection is inappropriate because visible amounts that are transferable by mechanical and airborne pathways would exceed acceptable limits for non-product surfaces. Accordingly, a risk assessment here is conducted focusing mainly on mechanical transfer and airborne transfer on non-product contact surfaces for highly potent products on the assumption that there are plausible pathways by which this material could be transferred to a product being manufactured in the same area.

Risk Management Tools

Among the tools introduced in ICH Q9, Failure Mode and Effect Analysis (FMEA) is employed herein. As introduced in ICH Q9, FMEA enables one to establish cost-effective countermeasures against risks by prioritizing risks and countermeasures by relative scores.

Hazard Level	Exposure Route	
Acceptable Daily Exposure (ADE)	Mechanical Transfer	Airborne Transfer
>10 mg/day	1	1
1 - 10 mg/day	3	1
0.01 - 1 mg/day	5	3
< 10 µg/day	7	5

The values of severity are defined:
10: Injury to a patient or employee
7: Cause extreme customer dissatisfaction
5: Something likely to result in a complaint
3: Minor nuisance resulting in no loss
1: Unnoticed and does not affect performance

Table A. Scoring of severity (example).

Risk Evaluation using FMEA for Process

A rule for scoring needs to be established prior to the risk assessment using FMEA and for this example as follows:

1. Unit of Evaluation: a typical part of a manufacturing system including process equipment, a building and HVAC system.
2. Potential Failure Mode: mechanical transfer and airborne transfer are taken as potential failure mode herein that could lead to exposure among the four routes of cross-contamination. (The others are mix-up and retention as discussed above).
3. Potential Effect(s) of Failure: patients exposure and presumed adverse effects.
4. Severity: scoring for the degree of the impact of exposure to patients and/or workers that is determined by the matrix of Acceptable Daily Exposure (ADE) and exposure route (Table A).
5. Potential Cause(s) of Failure: lack of control, ineffective control technique, human error and equipment malfunction are considered as the major factors among major causes.
6. Occurrence for Process: scoring for the degree of contamination occurrence which is attributable to process unit operations. That is defined by the matrix of amount of airborne/residue and degree of process. The example of scoring of occurrence is shown in Table B.
7. Current Controls (Detection): scoring is based on characters of failures (e.g., carry over, upset, and leakage) and its detection devise as shown in Table C. Failures are classified into 1. failure that is foreseeable and avoided beforehand by detecting its root cause, 2. failure that can be detected when it happens, and 3. failure that cannot be detected when it happens. Detection devices (automatic vs. manual) provide easiness and reliability on detections of failure and its root cause.
8. Risk Priority Number (RPN): RPN is a number obtained by multiplying scores of severity, occurrence and detection. Limits or zones need to be established for RPN by which acceptability and correction priority can be assessed.

Property of Operation / Amount of Airborne/Residue	Open Process		Closed Process
	Long Term	Short Term[1]	
Product Contact Parts MT (More Than) ADE or Cleaning Limit	10	7	1
Product Contact Parts NMT ADE or Cleaning Limit	1	1	1
Non-product Contact Parts[2] NMT ADE or Cleaning Limit	1	1	1

Notes:
1. Short term means less than a few seconds. The scoring table is based on the risk assessment table proposed in Baseline® Guide "Bulk Pharmaceutical Chemicals (Second Edition)".
2. In Table B, the scoring in case of MT cleaning limit at non-product contact parts is not defined. When containment system do function well, the above case could not be considered.

Table B. Scoring of occurrence for process (example).

FMEA Evaluation (Examples)

In this article, the following two case studies for risk assessment based upon Risk-MaPP are discussed:

Case Study 1: Weighing Process

Weighing of materials for an anti-neoplastic agent is conducted in a weighing isolator as seen in Figure 1. The inside of the isolator is kept under negative pressure. Air is supplied to the isolator from the process room through HEPA filters and double HEPA filters are located at the exhaust port. All of the necessary equipment and sealed material containers are transported into the isolator through the Pass

Failure Classification	Automatic Detection	Manual Detection
Foreseeable failure with its detectable root cause	1	3
Detectable failure (Not foreseeable)	5	7
Undetectable failure	10	10

Table C. Scoring of detection (sample).

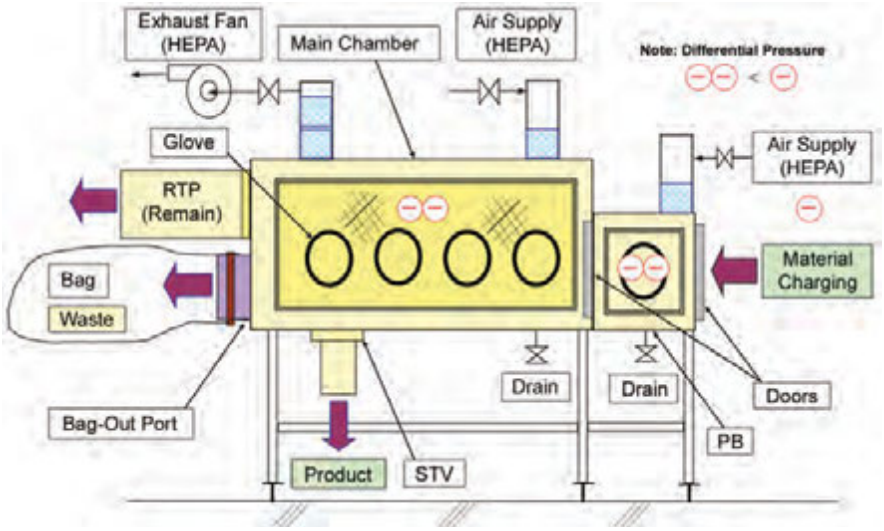

Figure 1. Diagram of a weighing isolator.

Box (PB) prior to weighing. After conducting predetermined weighing procedures in the isolator, the weighed materials are charged into a weighing container via the Split Butterfly Valves (SBV). Containers with leftover materials are put into a container via the Rapid Transfer Port (RTP) and kept in storage. Any wastes in the isolator are contained in a plastic bag through the bag-out port, removed using a safe-change system, and incinerated. When a series of process operations is completed, the inside of the isolator is manually cleaned with water by glove operation using spray guns.

Case Study 2: Compression Process

A typical rotary tablet press machine is used as an example in the second case study - *Figure 2*. The reason for this is because such tablet press machine is suitable for mass-production and can be easily automated. Also, the weight variation of each product manufactured by this machine tends to be small. Moreover, this machine contains generated dust and is easy to handle. These are many benefits for using this machine. A tablet press machine with rotary system is formed by several metallic punches and dies (upper punch, lower punch, and die) attached to a horizontal turntable. The turntable is rotated by a motor and while it rotates through 360 degrees, the following series of procedures is conducted continuously: 1. powder filling – a raw material powder is filled quantitatively into a cavity, 2. compression molding - compression and molding are conducted as the upper punches and lower punches rotate through the compression roll, and 3. product discharge.

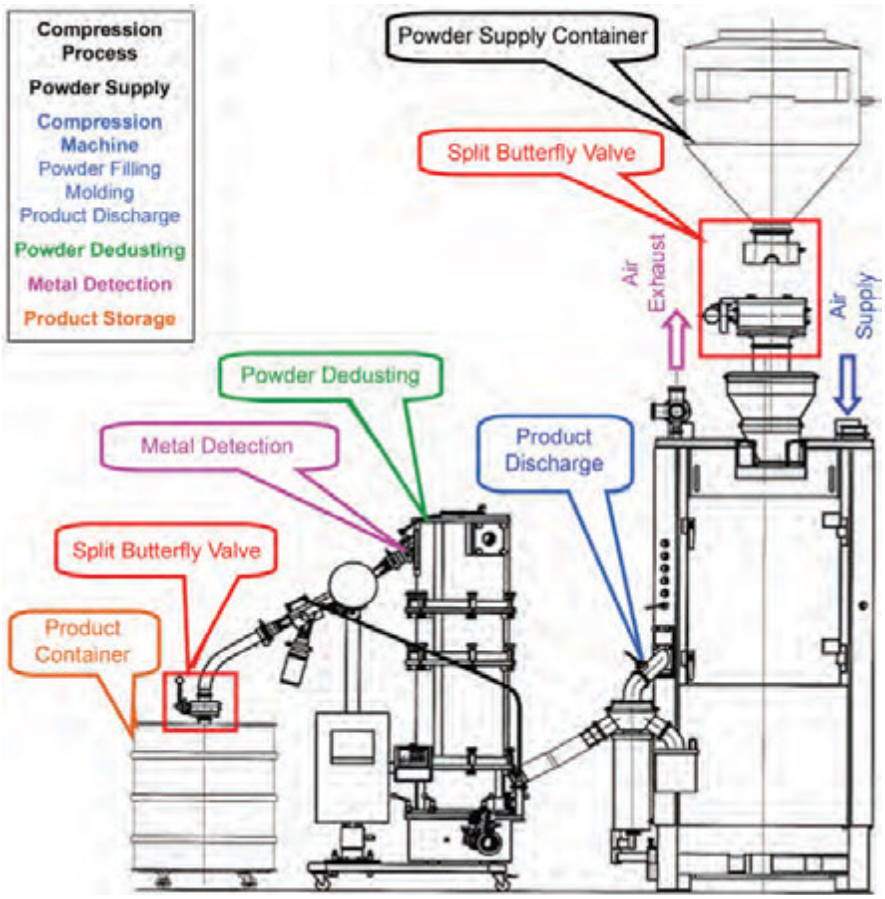

Figure 2. Diagram of a tablet press machine.

Materials are charged from the top of a device using supply containers and the tablet product is contained in a product container. Prior to implementation of any risk reduction measures, these containers had a split butterfly valve installed to enable containment. In this scenario, the tablet press machine itself has no device to predict risks, such as device to monitor the pressure inside a machine.

For the manufacturing of the anti-neoplastic products, the risk reduction measures for cross-contamination from a GMP standpoint was considered to ensure the safety of patients who take the pharmaceuticals.

Process/ Equipment Component	Process Step	Failure Mode	Potential Effects	Severity	Potential Causes	Quantity Amount	Property of Operation	Occurrence	Current Controls	Detection	RPN	Risk Reduction Measures	Severity	Quantity	Property of Operation	Occurrence	Detection	RPN
Weighing Isolator/ Pass Box	Charging	Airborne Transfer	Cross-contamination	5	Product residue inside the weighing room or on the ceiling is dispersed/suspend and then transferred into the next product via the pass box.	MT cleaning limit	OPEN (Short Term)	7	Failure Mode is Not Detectable	10	350	Thoroughly clean the inside of the weighing room. Confirm residues after every campaign manufacturing.	5	NMT cleaning limit	OPEN (Short Term)	1	3	15
Weighing Isolator/ Main Chamber for Weighing	Weighing	Mechanical Transfer	Cross-contamination	7	Compound adheres to the inside surface or the gloves and enters the next product through the weighing process.	MT cleaning limit	OPEN (Long Term)	10	Failure Mode is Not Detectable	10	700	Use electrolytic polishing to the inside surface finishes and change the window structure in order to reduce retentions. Change the glove structure to mitigate residues. Check the residues after every campaign manufacturing.	7	NMT cleaning limit	OPEN (Long Term)	1	10	70
Weighing Isolator/ Main Chamber for Weighing	Weighing	Airborne Transfer	Cross-contamination	5	Dust powder deposited on the exhaust HEPA filter falls from the filter and enters the next product.	MT cleaning limit	OPEN (Long Term)	10	Failure Mode is Not Detectable	10	500	Conduct integrity test of HEPA filters after every campaign manufacturing. Install a HEPA filter separated from the isolator's main unit.	5	NMT cleaning limit	OPEN (Long Term)	1	10	50
Weighing Isolator/ Charging · Discharging	Discharging	Airborne Transfer	Cross-contamination	5	Product residues inside the weighing room or on the ceiling is dispersed/suspend and then transferred into the next product through the connected surface of SBV.	MT cleaning limit	CLOSED	1	Failure Mode is Not Detectable	10	50	Put cover on the separated valve face surface of the SBV and wipe the valve surface with alcohol before connecting to the valves.	5	NMT cleaning limit	CLOSED	1	3	15

Table D. FMEA (weighing process, in case of ADE < 10 µg/day).

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Process/ Equipment Component	Process Step	Failure Mode	Potential Effects	Severity	Potential Causes	Quantity	Property of Operation	Occurrence	Current Controls	Detection	RPN	Risk Reduction Measures	Severity	Quantity	Property of Operation	Occurrence	Detection	RPN
Compression/ Supplying Equipment SBV	Change Material Container	Airborne Transfer	Cross-contamination	5	Dust/material deposited in the compression room or on the ceilings is dispersed/ suspended and transferred into a product powder which is under manufacturing through SBV connection port.	MT Cleaning limit	CLOSED	1	Failure Mode is Not Detectable	10	50	Put cover on the separated valve face surface of SBV Prevent transfer, Wash the inside of compression room, equipments, ceilings, walls and floors with water	5	NMT Cleaning limit	CLOSED	1	10	50
Compression/ Compression Machine	Compression	Mechanical Transfer	Cross-contamination	7	Compound adhere to the inside surface of a compression room or to wall and is transferred into a product under manufacturing during setting operation via operator's hands and clothing.	MT Cleaning limit	OPEN (Long Term)	10	Failure Mode is Not Detectable	10	700	Change to containment tablet press machine. Make adjustments to machines using the glove port so that there will be no direct contact with the powders or products. Use inflated packing to ensure that access cover is tightly sealed when it is closed, and install interlock to the doors to prevent unnecessary or unintentional opening. Opening of an access cover should be automatically detected and alarmed. Wash the inside of compression room, equipments, ceilings, walls, and floors with water. Change operator's clothing and shoes for every entry or exit from the room.	7	NMT Cleaning limit	CLOSED	1	10	70
Sampling/ Batch Sampler	Product Sampling	Airborne Transfer	Cross-contamination	5	Dust/material deposited on the outside surface of a tablet press machine is dispersed/ suspended through sampling port, vacuumed into equipment operated in a negative pressure and transferred into a product under manufacturing.	MT Cleaning limit	OPEN (Short Term)	7	Failure Mode is Not Detectable	10	350	Use sampling port equipped with valves to block the air flow and to prevent room air entering into the tablet press machine. Seal with liner tube or heat seal before discharging the sampling tablet. Contain and prevent the entry of an external air.	5	NMT Cleaning limit	CLOSED	1	10	50

Table E. FMEA (compression process, in case of ADE <10 µg/day).

The FMEA evaluation examples in the risk tables could occur in the pharmaceutical manufacturing process (Tables D and E).

Recommendations

In this article, the risk assessment methodology for GMP (quality) concerns regarding cross-contamination, especially airborne and mechanical transfer mode exclusively, was introduced. Its mock-application refers to the "application example" in Risk-MaPP, Appendix 14.

While this risk assessment using FMEA method was executed, some issues were identified. For instance:

- In an FMEA, the results are represented by Risk Priority Number (RPN) that locates and prioritizes areas where failure is likely caused.
- RPN is calculated by multiplying three scores: Severity, Occurrence, and Detection. When unsatisfactory RPN numbers are obtained, the area of risk reduction measures needs to be studied by examining these three scores, i.e., the factors of the RPN.
- The ADE is an important parameter in the assessment, particularly in determining Scores of Severity in our definition. Due to the fact that ADEs are scientifically developed values, Scoring of Severity helps to add quantitative meanings. The ADE values established by different toxicologists should be sufficiently close so as not to lead to different severity scores or control measures that might be needed or implemented.
- Verification data using the ADE applied over a standard surface area (e.g., 100 cm^2) consistent with the exposure pathways used in the risk assessment need to be collected to assess whether the risk reduction measures implemented as a result of the FMEA are adequate to control risks to the patient.

To judge, in FMEA, to find if the status is satisfactory, it refers to the predetermined RPN score or zone for satisfaction. The score of satisfaction shall be established by Senior Management and shall not be changed unless it becomes inappropriate and needs to be adjusted to reflect the results for a certain number of projects.

This article only covers the risk assessment using FMEA limited to GMP concerns. Those for IH concerns also can be conducted. These case studies demonstrated very clearly that FEMA was very useful to conduct risk assessment for process and premises in alignment with Risk-MaPP. Thus, the project which applies FMEA to the actual situation was established and now has been studied. The results from this study will be released in a report in near future.

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Master Planning the Legacy: Meeting Good Manufacturing Practices While Using Existing Pharmaceutical Manufacturing Facilities

by Eric Bohn, AIA

This article explores some of the challenges and opportunities that can be encountered when bringing legacy facilities into compliance with current good manufacturing practices.

Managers of legacy pharmaceutical manufacturing facilities continually struggle against an implacable enemy, the ever evolving triumvirate of aging infrastructure, improvements in technology, and the evolution of good manufacturing practices. Eventually, legacy facilities are burdened with outmoded infrastructure, equipment that has reached the end of its useful life, and production facilities that have not keep pace with current standards for good manufacturing practices.

Experienced facility designers often see this manifest itself with disjointed and circuitous material and personnel flows and inconsistent and isolated gowning procedures and locations. In older facilities, incremental building additions and changes in manufacturing processes and equipment tend to create less than optimal product flows.

Establishing and monitoring current Good Manufacturing Practices (cGMPs) occurs on an international basis. The China Food and Drug Administration, the European Commission for the European Economic Area, Central Drugs Standard Control Organization in India, and the Food and Drug Administration in the Unites States represent some of the major markets with which drug companies need to comply.[1-4] In addition, numerous other regions and individual countries have their own agencies. While the International Conference on Harmonisation is working "toward achieving greater harmonization in the interpretation and application of technical guidelines and requirements for pharmaceutical product registration," there are still numerous specifics that need to be considered depending on the countries being served.[5] Regardless of the regulatory agency involved, changes in the pharmaceutical industry are driven in large

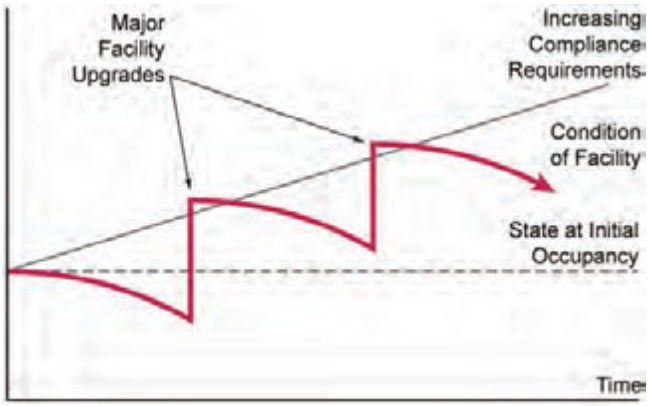

Figure 1. Graph illustrating the effort needed to stay current with aging infrastructure, improvements in technology, and the evolution of good manufacturing practices.

measure by new technologies. Recognizing this, the FDA states on their webpage "Facts about Current Good Manufacturing Practices (cGMPs)":

> *"...the "c" in cGMP stands for "current," requiring companies to use technologies and systems that are up-to-date in order to comply with the regulations. Systems and equipment that may have been "top-of-the-line" to prevent contamination, mix-ups, and errors 10 or 20 years ago may be less than adequate by today's standards."*[6]

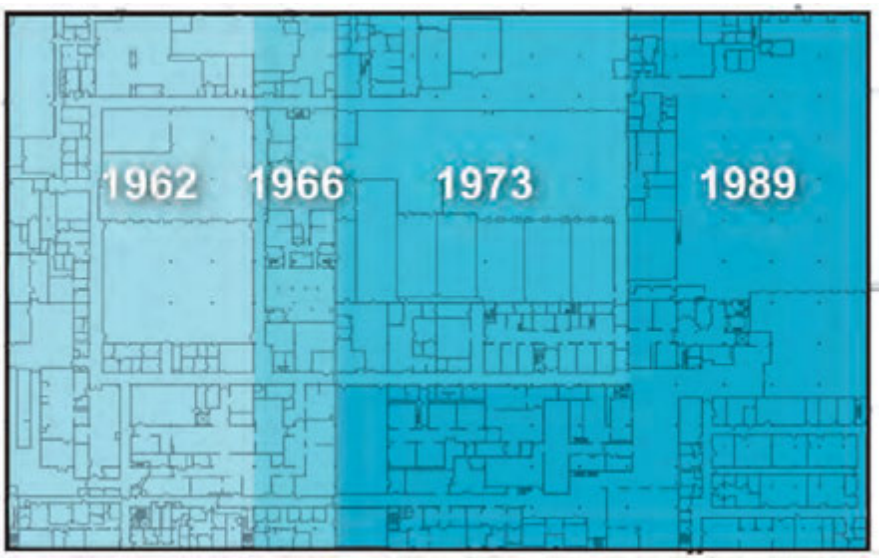

Figure 2. Example of an OSD facility first erected in 1962 that more than tripled in size over 30 years and is still in use after 60 years.

Faced with these competing pressures, manufacturing managers often opt for the expedient solution of spot renovations to resolve immediate problems. However, this approach can exacerbate existing deficiencies especially those related to material handling and personnel circulation. With the potential for lower labor costs and an easier regulatory and environmental climate overseas, management has many options when faced with a less then optimum existing facility. The choice to invest in a new "greenfield" facility in lieu of a legacy facility can be very attractive.

However, while legacy pharmaceutical manufacturing facilities present challenges for facility managers, they also contain special opportunities to add value to corporate productivity. A cost effective solution to the deficiencies inherent in legacy facilities is to develop a program based on careful planning to reorganize and renovate the existing facility. Analysis should focus on identifying effective measures that reduce waste and redundancy, maintain facility compliance with cGMPs, and – most importantly – enhance productivity.

This article will explore some of the challenges and opportunities that can be encountered when bringing legacy facilities into compliance with current good manufacturing practices. The principles for preparing a master plan remain the same regardless of the agency or agencies having jurisdiction. Through development of a comprehensive master plan for reuse and renewal, the legacy pharmaceutical manufacturing facility can be advantageously positioned to meet long-term goals for sustainable operations into the future.

Definition of a Legacy Facility

Legacy facilities are defined as those existing manufacturing facilities that have developed over an extended period of time, and in the process, have accrued incremental changes from their original configuration. One Oral Solid Dose (OSD) facility recently renovated was first constructed in 1962 and then expanded in 1966, 1973 and 1989, more than tripling in size over a 30 year period. Another facility was originally built in 1971 and was enlarged with six major additions by 2002. These facilities, still in use today, are more than 50 years old. They expanded because of their success and profitability. Changes were made to create more capacity and space for new product lines, interior spaces and the movement of material and personnel were repeatedly reorganized, new production equipment added, and all the while the expectations for GMPs continued to evolve.

Technological improvements drive change as new manufacturing processes and instrumentation lead to reconfiguration of production lines and material handling. Over time, incremental changes result in a facility that may have multiple additions and random placement of production functions that result in circuitous circulation patterns. In a generic pharmaceutical facility, when additional space for granulation was needed, a new suite was built in the adjoining warehouse. In another facility, a new bioreactor process was built in a warehouse that was not even part of the building devoted to production. In both cases, lack of integration into existing flows increased the handling and staging of material, eroding the efficiency of the operation.

Incremental changes that occur in isolation can reduce effectiveness of the entire facility: a change in one area can lead to bottlenecks or crossed movement of material and personnel. A common principle of most GMPs is the need for the appropriate sequence of operations, adequate staging and flow of materials and personnel to prevent mix-ups or contamination.[7-10] If these challenges to a legacy facility are

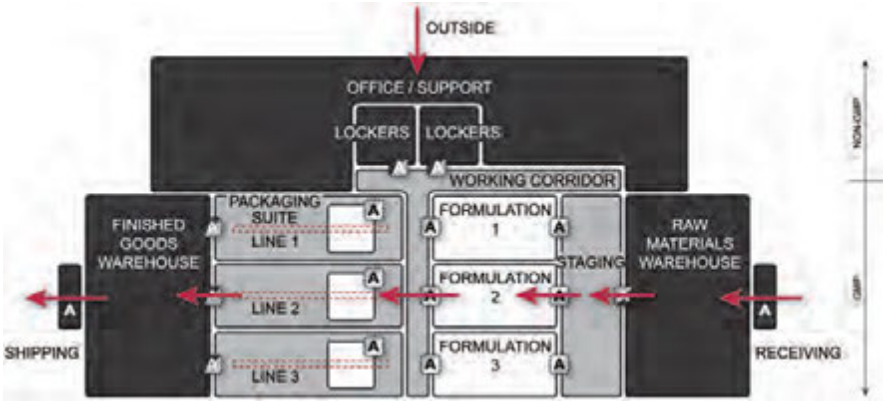

Figure 3. Clearly defined circulation pattern that is sequential and reinforces an efficient operation.

ignored and not corrected, it will increasingly become at risk of being identified by the regulating agencies as in need of correction.

Business Case for Maintaining Legacy Facilities

The pressures of running and maintaining a legacy facility are sufficiently challenging without the worry of revitalizing an existing facility to accommodate new products and technologies. But an established facility has many embedded attributes that can make it attractive as a vital part of a company's future.

Most obvious among these is the existing capital investment: established facilities embody many years of investment. "Bricks-and-mortar" construction costs for the building structure, utilities and other infrastructure are all realized and readily available for future contributions. Capital costs for equipment have already been invested and the production operations well established.

A less obvious benefit is the staff at an existing facility. Typically, the greatest operational expense of any facility is the people who work there. The employer accrues intangible benefits from their investment in personnel in terms of training, experience and knowledge. This includes the collective memory of the facility's operations staff, their knowledge of the particulars of the manufacturing process, and the spirit to succeed that comes from working with like-minded people committed to a common goal.

The established logistical infrastructure of a legacy facility is also value laden. It is easy to overlook just how integral the location of every facility is to its operations. Support services, vendors, material suppliers, shipping/transportation services, have integrated the specifics of a location, including established procedures, into the delivery of their services. While the supply chain that supports a site can change, it is disruptive to do so. The risk of interrupting production is mitigated to the extent that continuity can be maintained.

All these resources can be assigned a latent value when an existing facility is revitalized to play a crucial role in a company's global supply chain. It takes years for a new facility to shake out the many logistical issues that make a facility run smoothly.

Development of the Legacy Facility Master Plan

Problems with Legacy Facilities

Legacy facilities present many challenges to maintaining effective and compliant operations. As a result of incremental growth and periodic investments in new technologies and equipment, legacy facilities often become a tangle of inefficiencies. Several key areas of concern include the crossing of flows, the danger of cross contamination, the aging of critical utilities, changes in equipment and the introduction of new products:

1. **Flows:** manufacturing facilities ideally contain clearly defined circulation patterns that are sequential and reinforce an efficient operation. Raw materials are assembled from the warehouse, enter into the production process, and ultimately emerge as finished goods in a linear sequence that minimizes or eliminates crossing of the work-in-progress and the corresponding risk of mix-ups and contamination. Over time, and as a result of incremental additions and internal reorganizations, circulation patterns that originally followed a logical path through defined yet isolated zones can become compromised by changes that may have developed as a result of localized alterations and equipment changes. A common symptom of this condition is when a simple and clear gowning sequence does not exist. Facilities exist where corridors are accessed by personnel in both gowns and in street clothes. Such lack of segregation of activities is a strong indication of a problem.

2. **The Dangers of Cross Contamination:** problems of cross contamination can occur in two principle areas: air systems and product handling. Incremental additions to buildings or repurposing of existing spaces from one activity to another may result in air distribution and handling systems that lack adequate segregation between activities. This mixing of air systems, often resulting from an expedient modification of an existing system, can lead to air borne contamination of raw materials or in-process products. Problems also can arise when raw materials or finished products are mixed between process streams leading, at best, to confusion and at worst, product contamination. Modern systems of bar coding and serializa-

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tion help to significantly reduce the risk of cross contamination from handling errors, but they are not foolproof. Random adjacencies and scattered production suites that are often encountered in legacy facilities are still problematic.

3. **Aging Critical Utilities:** a third major category of problems associated with legacy facilities include those related to aging infrastructure, equipment, and utilities. When initially constructed, the legacy facility was likely designed and constructed with "state-of-the-art" environmental controls, electrical equipment, production machinery and their related controls, telecommunications and data services, and business operations technology. As equipment ages, breakdowns become inevitable. Over time, mechanical systems and control equipment degrade at a relatively predictable rate, and replacement can be anticipated. Incremental additions to the building structure, localized renovations for new product lines, piecemeal upgrades to product manufacturing systems or utilities, or localized system replacements can leave the legacy facility with a patchwork of mismatched and incompatible equipment. Although routine and timely maintenance can delay the inevitable, there comes a time when equipment has reached the end of its useful service life and must be replaced.

4. **Technology Advances:** technological advances and improvements over time can rapidly lead to obsolescence of existing systems and equipment and hinder the facility's efficiency, effectiveness, and ability to maintain compliance with cGMPs. As more efficient production, control, and handling equipment becomes available, the challenge becomes one of maintaining competitiveness and profitability within a legacy facility. Similarly, existing building utility systems and infrastructure become less efficient over time, and newer models often incorporate advances in energy efficiency, flexible operating controls, and more efficient use of resources. Thus, energy consumption and cost of goods remains hostage to outdated technology with little opportunity to effect enhancements and cost reductions that accrue from bringing on line more efficient equipment.

5. **New Products:** the Marketing Group is always reworking existing products, and new products are periodically introduced to an existing facility. Sometimes these changes can be accommodated within the existing equipment and infrastructure. But eventually the problem becomes one of how to fit new equipment and processing suites into the current footprint leading to a significant cascade of compliance issues within a single facility. If not carefully considered and located in a manner that reinforces or even improves the integrity of existing flows and infrastructure, serious compromises can result.

Master Plan as Solution

Legacy pharmaceutical manufacturing facilities, despite any outward appearance of systemic obsolescence and problems, contain significant resources in the form of in-place construction, knowledgeable human resources, and capital investment that cannot be dismissed. Continued use and rehabilitation should be desirable and attractive. A conventional and expedient practice of responding to changes on a case-by-case basis, in the most expeditious manner and at the lowest cost, too often sets the stage for developing inefficiencies.

A master plan presents the opportunity to develop a vision for the future. For the legacy facility, the master plan can establish a direction to reinvent a facility that will remain sustainable, viable, productive, successful, and profitable. The discipline of preparing a master plan facilitates the comprehensive evaluation of the strengths and weaknesses of the legacy facility and seeks to identify opportunities and constraints. From the analysis of the legacy facility, the master plan will identify specific improvements that will best implement the goals of streamlining materials flows, personnel circulation, and improving the condition of critical utilities. Creating a matrix for future projects may require enlarging the scope of individual projects to include work on areas adjacent to the area of immediate concern. Such a matrix can provide a coordinated framework for numerous smaller projects that, over time, will work toward the broad recommendations of the master plan.

There are a number of different ways to develop a master plan; however, the major components are the same regardless of the local or regional cGMPs that are being accommodated. These components include a thorough understanding of the existing facility and its operations, the identification of the applicable GMP principles that will be applied at the site, a space program, and finally, the development of the plan itself. This final step can stand by itself as the over-arching vision for the facility, or through supplemental plans that can be created; the master plan can anticipate details of the phasing and progressive implementation that leads to the final configuration of the facility.

Existing Building Analysis: the initial step is to understand the existing facility and its operations in terms of current good manufacturing practices. To capture and evaluate the critical issues, it is necessary to gather and develop a database that will help visualize existing conditions. These include:

- Flow diagrams for materials, personnel and waste

- Hygiene zoning diagram(s) identifying areas of open product, air classifications, and risk of cross contamination
- Diagrams documenting existing locations and procedures for the gowning

GMP Principles: early in the process of developing a master plan, it is important to work with the appropriate stakeholders at the facility to identify the good manufacturing practices that will have authority over facility operations. These concepts will provide basic criteria by which to evaluate options and to inform the final master plan. Issues to be addressed include:

- Defining the different zones of work using concepts of protection levels 1, 2 and 3(11), ISO air classification, white/grey/black/green or other agreed standards.
- Establishing concept for transitioning between different hygiene zones (i.e. airlocks).
- Establishing principles for gowning and entry to different hygiene zones.

Programming: a programming effort is necessary to establish the overall facility goals and vision, the space and functional requirements, and the overall equipment, utility and operational requirements. These criteria need to be aligned with corporate business and marketing strategies and should aim to position the facility to accommodate future changes and/or growth. Once gathered and quantified, this information can be used to develop a space program for the overall facility. The space program should, at a minimum, identify the following information:

- Physical space requirements including room/suite sizes
- Projected growth over time
- Major equipment needs
- Required utilities and services for the space/suites and equipment
- Room finish criteria
- Room HVAC criteria
- Room lighting criteria
- Room plumbing requirements
- Pure water needs
- Any other specialty needs

Plan Development: using all the information previously gathered, a final facility master plan is developed. The resulting plan will explore layout options, constructability, implementation logistics, and relative project costs (including construction costs, design fees, approvals and permitting costs) for the several options generated. Potential layouts are tested by overlaying the various material, personnel, and waste flows.

Discussion of the merits and deficiencies of the plan options will lead to a recommendation for a preferred master plan for the facility, which should also include the follow diagrammatic information:

- Material Flow Diagram
- Personnel Flow Diagram
- Waste Flow Diagram
- Hygiene Zoning Diagram

The master plan can be detailed down to the level of individual rooms or can be more general and visionary in nature by addressing larger blocks of space or functional areas. In addition, the overall master plan can be further broken down to illustrate the anticipated phasing that sets a framework that can be used to achieve the master plan.

Recommendations identified in the master plan can be implemented as opportunities arise and should go beyond the simple expedient solution. The resultant reorganized legacy facility will benefit from easing of maintenance and operational activities, better materials and personnel flows, clear gowning protocols, simplification of infrastructure distribution systems, and more effective Standard Operating Procedures (SOPs).

Common Objections to the Legacy Facility Master Plan

It is human nature to look at short time horizons, such as the next quarter or the next year, without taking the time to look at the broader life-cycle of a facility. In the fast paced market place of product delivery, it is often critical to implement new production strategies or new product lines in as short a period as possible to accelerate return on investment. Some common objections to taking the time to develop a master plan for the legacy pharmaceutical manufacturing facility include:

1. **Corporate Pressures:** site management often states that corporate management doesn't understand site conditions and is always pushing to have things done faster and sooner with less labor and little disruption to the manufacturing process and production schedules.

2. **Time:** it is sometimes argued that site management is already overburdened with day-to-day operational duties. Taking time to meet with design professionals to evaluate legacy facility operations will take away from core responsibilities. The incremental time to implement meaningful renewal of the legacy facility also may be considered a negative, as episodic changes to address specific issues can sometimes be implemented rapidly with little apparent disruption to existing facility operations. However,

over time, the accrual of small inefficiencies can lead to increased potential for non-compliance.

3. **Money**: it may be claimed that money spent on a master plan is not money wisely spent. This simple accounting often does not include lost time and profit due to inefficiencies that accrue in the legacy facility due to the additive nature of previous alterations. Incremental expenses are also incurred from addressing problems reactively rather than proactively.

4. **Flexibility:** some fear that adopting a master plan will in some intangible way restrict or limit the ability to rapidly respond to changes in technology, production equipment, or the implementation of new products. There is the illusion that business as usual represents the greatest flexibility, even if it means having to work around accrued inefficiencies.

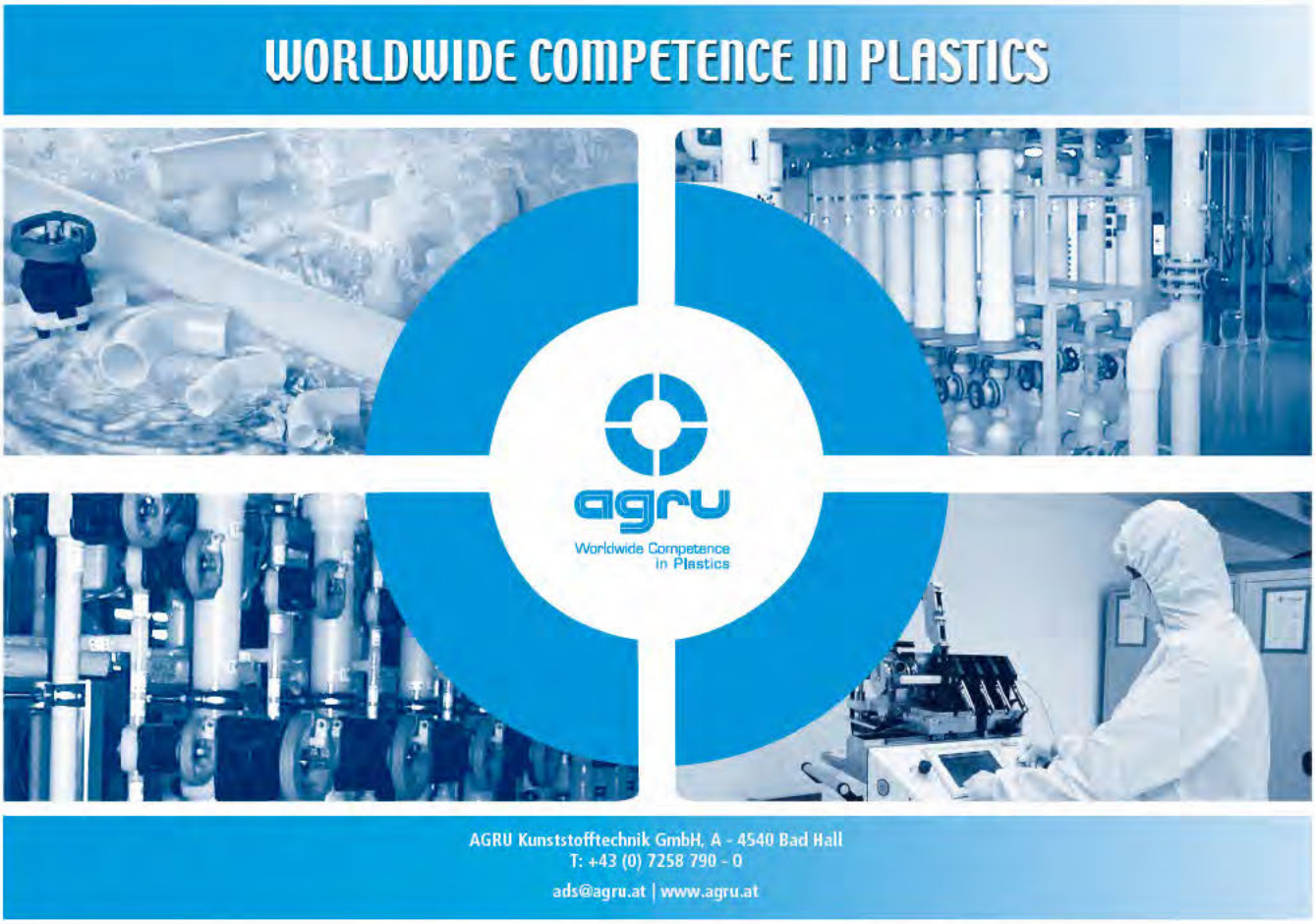
5. **Tradition and Convention:** the "that's-the-way-we've-always-done-things-around-here" mentality. While this is human nature, such an attitude works counter to the need to sustain successful operations into the future.

Conclusion

The world outside the legacy pharmaceutical manufacturing facility continues to change every day. It is essential that new developments are tracked to identify potential issues and opportunities, and areas for improvement. Like developing a "wish list," prospective improvements should be prioritized, with highest priority given to those areas of operations or infrastructure that represent the greatest risks to ongoing and future operations.

Legacy facilities represent a significant investment in "bricks-and-mortar" structure and infrastructure, production equipment, and trained personnel. By definition, they have been highly productive and profitable and retain the potential – with careful intervention – to remain so into the future. Long time employees acquire important and valuable experience with the facility, its operations, systems, and existing equipment, and are adaptable to new methods and technology.

Essential to a rational and practical approach to developing a sustainable strategy for facility renewal is the investment in time and effort necessary to take a comprehensive overview and assessment of the entire facility. The recommendations of a master plan will serve as the guide for elimi-



nating bottlenecks and crossed flows, reducing isolated production and handling areas that foster mix-ups of materials and products, and for planning for sequential replacement of critical infrastructure utilities. Key goals will include:

1. Modernization of equipment and facility infrastructure
2. Enhance staff efficiency and effectiveness with a focus on saving time performing tasks and functions
3. Improve the efficiency of product and materials flows throughout the entire process from handling of raw materials to finished goods
4. The possible reduction of square footage of facility devoted to manufacturing
5. Create capacity for higher production and lower cost of goods

For a legacy facility to continue to grow and evolve sustainably into the future, the master plan for the facility must look forward in 10 to 20 year renewal cycles that correspond roughly with cycles for upgrading and replacing building systems and equipment, and with changes in production technology. Master plans are not meant to be static documents: assumptions and conclusions must be reevaluated in light of changing priorities and updated at regular intervals as part of a strategy to extend the life of the facility, to create an environment for flexible growth through renewal, and to sustain and enhance profitability.

Through the discipline of preparing a master plan, corporate and site management will have a forum by which to identify problem areas, evaluate and assess options to remediate problems, and reach consensus and agreement on committing resources to implement a program for phased alterations and improvements. This collaboration also can foster a framework for focusing on "big picture" issues affecting a legacy pharmaceutical manufacturing facility to maintain effective and efficient operations. By following a disciplined course of phased and sequential renewal, the legacy pharmaceutical manufacturing facility can be brought incrementally up to current standards and manufacturing efficiency to ensure that long-term profitability can be maintained within a framework of sustainable facility operations.

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Eric Bohn, AIA started his career as an architect in 1980 and has developed an extensive expertise in the design and construction of pharmaceutical facilities. Since joining Jacobs/Wyper Architects, LLP, Bohn's experience has focused on the design of laboratories, pharmaceutical, biotech and medical device facilities, encompassing both new and existing cGMP and GLP facilities. He has helped many clients overhaul their legacy facilities to ensure compliance and increase value by improving flows, efficiencies and the integration of new technologies. Bohn was the architectural project manager for Merck's Global Clinical Supply Facility which was awarded the 2011 ISPE Facility of the Year Award Winner for Facility Integration. He can be contacted by telephone: +1-215-985-0400.

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The Efficacy of Ozonated Water in Biofilm Control in USP Purified Water Circulation and Storage

by Erika Hanley-Onken and Nissan Cohen

This article presents a case study for the use of ozone to reduce the amount of biofilm contaminant in a pilot UPW production and delivery system designed to represent typical large 316L stainless steel systems in biopharmaceutical companies.

Storage and distribution systems for water and water-based fluids are both critical and ubiquitous in every industry, geography, and culture. Large scale industrial water handling systems require water storage and distribution for a range of applications from simple thermal control (cooling and heating systems) to Purified Water (PW) production and delivery.

For more than 40 years, manufacturers of pharmaceutical products have been concerned about potential microbial contamination of their water systems. The action and alert limits commonly cited in literature are based on sampling of the water from a use point, inoculation and incubation of a nutrient plate, and counting the resulting bacteria. These point-of-use samples are simply the planktonic concentration of the bacteria in the water and may not represent other contamination sources, i.e., biofilms.

This article provides a case study for the use of ozone to reduce the amount of biofilm contaminant in a pilot PW production and delivery system designed to represent typical large 316L stainless steel systems in biopharmaceutical companies.

While there are a number of potential sources of contamination in storage and delivery systems for purified and sterile water, one of the most common problems facing PW production and delivery is the prevention and removal of biofilms. First described by Henrici[1] and Zobel[2] more than 60 years ago, these tenacious thin films form on almost any natural or synthetic surface and wherever surface-associated microbes are present. Once established, biofilm-producing microbes Excrete Polymeric exopolysacharrides (EPS) film that cannot be effectively removed using conventional antimicrobial Reagents.[3,4] The EPS provides a matrix where nutrients are retained and microbes can thrive, thereby continuously contaminating the PW storage and distribution system. Biofilms occur in a wide variety of systems that can range from the biological (e.g., plant life, gastrointestinal tracts, etc.) to the highly technological (e.g., medical and dental implants).[5-12]

The removal of biofilms from the wetted surfaces of PW systems is thus a prerequisite for the maintenance of high purity water quality in many industries. Elimination of this source of microbial contamination is critical, but can be exceedingly difficult.

Studies have shown that the chemical composition of biofilm matrices varies depending on both the source of the originating microbial contaminant and the environment within which the biofilm grows.[3,13,14] This compositional variability makes targeted destruction of biofilms difficult, encouraging the use of non-specific treatments that can address its heterogenity. Conventional antimicrobials may not penetrate the protective EPS film, and microbes that in planktonic form can be controlled through the use of a particular biocide may instead become extremely resistant to decontamination when resident within a biofilm matrix. Biofilm removal treatments

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also must be biocidal, as removal of the biofilm's EPS matrix liberates the underlying colonizing microbes. Unless destroyed, these underlying microbes will migrate and reestablish at new sites, maintaining the contamination of the water system.

These prerequisites for biofilm control have resulted in a preference in most industrial settings to employ strong oxidant chemistries for biofilm mitigation and removal. Typically, chemicals such as chlorine, organochlorides and peroxychlorides have been preferred. Recently, drawbacks with these conventional approaches, such as water contamination concerns, tightening environmental regulations, and chemical costs, have led different industries to explore the use of ozonated water for the removal of biofilms and destruction of microbial contamination.[3]

Ozone (O_3), an unstable allotrope of oxygen, reacts rapidly with most hydrocarbons to effectively destroy biofilms, microbes, and organic residue material within these films.[15] As the strongest commercially available oxidant, it has a disinfecting strength 3000 times that of chlorine. At appropriate concentrations, ozone injected in water destroys all microorganisms, viruses, oocysts, and pyrogens, and reduces Total Organic Carbon (TOC) by chemical oxidation. Ozonated water leaves no chemical residues, unlike other chemical purification procedures, and in ambient water ozone reverts back to oxygen within approximately 20 minutes. Any excess or residual ozone also can be easily and immediately destroyed through exposure to Ultraviolet (UV) irradiation according to:

$$2O_3 \xrightarrow[h\nu]{} 3O_2$$

Many treatments can effectively reduce microbial contamination in a water distribution system; however, for PW, it is critical that all microbial contamination be removed. Feinstein, in an article published online in ALN Magazine,[16] provides effective definitions for sanitization, disinfection and sterilization:

> *"**Sanitization** will offer a contamination reduction or bio-burden reduction of 99.9% or 3 log (10^3). This means that we can expect that out of one million microorganisms, a sanitizer will destroy approximately 990,000 of the organisms leaving behind many viable microorganisms to reproduce. Sanitization is accomplished by utilizing chemicals and gels to achieve this level of cleanliness*
>
> ***Disinfection** will offer a bio-burden reduction of 99.99% and up to 99.999% or up to 5 log (10^5). This means that we can expect that out of one million microorganisms, a disinfectant will destroy up to 999,990 of the organisms leaving behind very few, but still some, viable organisms. Disinfection is accomplished by utilizing many different chemicals or ultraviolet light.*
>
> ***Sterilization** is the statistical destruction of all microorganisms and their spores. This is defined as 6 log (10^6) or a 99.9999% reduction. Statistically, this definition is accepted as zero viable organisms surviving. Sterilization is accomplished via several methods including ionized hydrogen peroxide or other hydrogen peroxide based solutions, high heat, ultraviolet light, ozone, radiation, and chemicals (chlorine, formaldehyde, glutaraldehydes, etc.)."*

For PW production, especially for pharmaceutical applications, the latter category should be achieved within production, storage and distribution systems to ensure that planktonic biofilm microbes are not sampled, potentially providing increased readings for tested parameters. Strong continuing mitigation of biofilm may ensure compliance of the water system.

The advent of ASTM standard E2500[17] removed a number of impediments to the implementation of ozone-based purification in pharmaceutical manufacturing, encouraging improvements in Process Analytical Technology (PAT) through well-documented, robust and flexible manufacturing capabilities. Since then, the confluence of continuously rising energy costs, process simplicity and political pressure for lower pharmaceutical prices has helped define newer technologies, such as ozone, to replace heat shock (hot water sanitization, steam, etc.) and chemical disinfection using chlorine, chlorides, peroxides, etc. Simple injection and mixing of gaseous ozone into the water is sufficient to produce concentrations suitable for microbe-free PW. Ozone is both safe and economical to use since it can be reliably generated on-site as needed, avoiding the handling and costs associated with strong oxidant transportation and storage. It is generated at ambient temperature and is soluble in ambient temperature water, increasing ease of operation. The infrastructure requirements for thermochemical sterilization and subsequent decontamination are significant and the use of ozonated water can greatly reduce capital, operations, and maintenance costs of water treatment.[18]

This study describes tests in which a pilot scale USP purified water storage and distribution system was challenged using a minimum of 10^6 logs of *E. coli* (ATCC #8739) that were either inoculated into the recirculating purified water system in planktonic form (Challenge Test A) or established as biofilms on stainless steel coupons placed in the distribution system (Challenge Test B). The efficacy of ozonated water treatment for *E. coli* biofilm removal and system sterilization was tested by ozone treatment of these contaminations at three different ozone concentrations at three time periods. Resulting counts of test Colony-Forming Units (CFUs) determined the amount of log reduction of the microbial contamination.

Figure 1. The full experimental test skid and water system used in this study.

Equipment and Procedures

Figures 1 and 2 are photos of the purified water storage and distribution system employed in this study. Figure 3 provides a schematic diagram detailing the components of this experimental test bed. The purified water storage and distribution skid, consisting of a 30 ft, 316L stainless steel water loop, was designed and manufactured for this study. Configured within the loop were an automated integrated water ozonation system, a 200 liter closed storage tank equipped with an ozone destruct unit, a recirculation pump, and a sample coupon rack for the sterile stainless steel coupons. Treatment products used to create Deionized (DI) process water, a conductivity meter, and other non-ozone related components were supplied for this study. For all references, see manufacturers' identification at the end of this article.

The ozonated water within the loop was monitored for ozone concentration using an external dissolved ozone concentration monitor with a range of 0 to 10 ppm. A separate conductivity meter measured the water's conductivity. The integrated automated water ozonation system provided up to 30 gpm (113.6 liters per minute, lpm) of ozonated USP PW by an ozone generator fed by an oxygen concentrator. The automated water ozonation system comes equipped with standard components of an ozone generator, Pressure Swing Absorption (PSA) oxygen concentrator, dissolved ozone monitor (0 to 10 ppm range), and process water flow meter, with integrated degas capability and safety monitoring. The unit's optional UV destruct attachment was included for purposes of this evaluation.

Two test procedures were employed in the study. In the first (Challenge Test A), the recirculating ozonated water was inoculated to achieve at least 10^6 CFU/mL of *E. coli* in the system. After inoculation the system was run with an ozone concentration of 2 ppm in the process water, and the bacteria contamination level was monitored. In the second procedure (Challenge Test B), six duplicate stainless steel coupons were aseptically inoculated with at least 10^6 CFU/coupon of *E. coli*. After the formation of a surface biofilm of at minimum 10^6 CFU/coupon, the coupons were placed into the coupon holder in the recirculating ozonated water loop. Coupon decontamination was evaluated at three separate ozone concentrations of 0.5, 2, and 5 ppm respectively. Coupons were collected for testing for *E. coli* after 2, 5, and 10 minutes exposure to each of the various concentrations of ozonated water. Each experiment was performed with new coupons inoculated according to the same procedure. An additional coupon experiment with no ozone (0 ppm) was run to establish a comparative baseline.

Methodology

Pilot USP PW Water Storage and Distribution System Testing

Initial Test System Sanitization

Prior to initiation of the test series, the USP PW water system was twice drained and refilled with fresh DI water to purge any contaminants, and the ozone monitors were recalibrated to a zero setpoint. The system was then sanitized by ozonat-

Figure 2. Close-up of the storage tank and coupon sampling system.

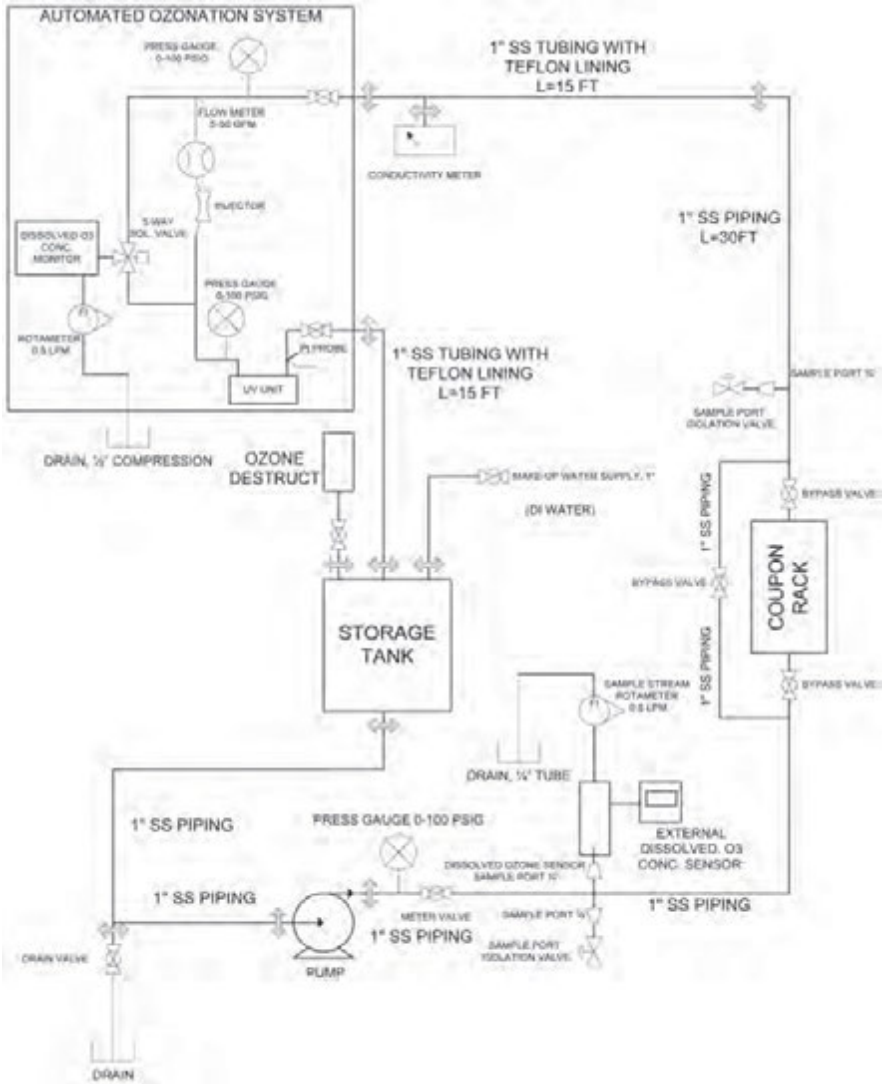

Figure 3. Schematic of the purified water storage and circulation test bed around the automated ozonation system.

ing the recirculating water for one hour using the automated ozonation system at a setpoint of 5 ppm. After the hour-long sanitization, the ozone generator was turned off and the UV was activated to destroy any residual ozone. The system then ran for an additional 30 minutes with the UV destruct operational to lower the ozone concentration to the lower measurement limit of the ozone monitor (< 40 ppb). At this point, the water was sampled and its conductivity measured to ensure the water met USP PW criteria as described in USP <1231>, of Heterotrophic Plate Count (HPC) < 100 CFU/mL, TOC ≤ 500 ppb, and conductivity < 1.3 µS/cm. Figure 4 shows the ozone profile for this initial sanitization as measured at the ozonation system.

After an initial rapid increase of the dissolved ozone concentration in the recirculating PW, the temporary concentration drops briefly as the automated ozonation system adjusts the ozone generator power to achieve the optimal long-term setpoint. After the time period is completed, the final measurable ozone is quickly destroyed by turning off the generator and activating the UV destruct.

Challenge Test A: Planktonic E. coli Testing

After the production of USP PW within the water storage and distribution system had been confirmed, the efficacy of ozonated water for the decontamination of planktonic *E. coli* was tested (Challenge Test A).

In this initial test, baseline water samples were first obtained and measured. The UV destruct was then turned off and an inoculums preparation volume appropriate to achieve 10^6 CFU/mL concentration of *E. coli* in the USP water recirculation loop was aseptically transferred to the system using the internal sampling port with a sterile funnel. Following the transfer, water was allowed to circulate for approximately 5 minutes at 12 gpm to ensure uniform distribution of the inoculums throughout the system. The challenge populations of *E. coli* within the system were determined by aseptically collecting 120 mL of system water from the drain port after the coupon rack and analyzing the sample. Samples were refrigerated immediately following collection. The system water control samples were tested by preparing dilutions in PB (Phosphate Buffer) water and plate dilutions of 10^{-1} through 10^{-6} to Tryptic Soy Agar (TSA) in duplicate. The plates were incubated and *E. coli* counts determined as described above. The system challenge

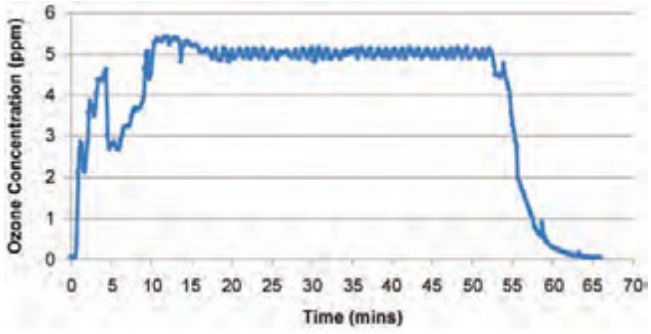

Figure 4. Ozone concentration profile at generation system return – initial system sanitization at 5 ppm.

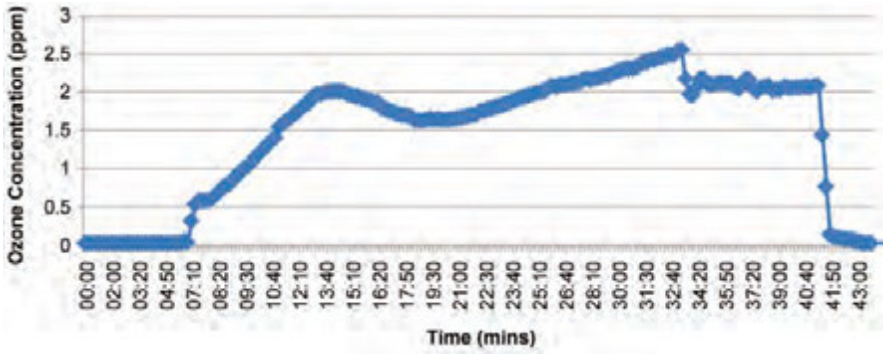

Figure 5. Ozone concentration profile during the planktonic system challenge test (Challenge Test A) – 2 ppm ozone challenge.

analysis had to exhibit at least a 1.0 x 10^6 CFU/mL population of the challenge organism for acceptance.

The inoculums for these tests were prepared as follows: 4L of Trypticase Soy Broth (TSB) was inoculated with *E. coli* (ATCC# 8739) and incubated at 32.5 ± 2.5°C for 48 hours. The inoculum population in the TSB was confirmed by preparing dilutions in sterile Phosphate Buffer (PB) water and plating to Tryptic Soy Agar (TSA) plates. These plates were incubated at 32.5 ± 2.5°C for 18 to 24 hours and the colonies counted to confirm the concentrations in the inoculums. Once the control population of *E. coli* was established within the water storage and distribution system, ozonation tests were performed. Following collection of a control sample, the automated ozonation water system was turned on and set to achieve a concentration of ppm ozone. Figure 5 shows the ozone concentration profile over the duration of the test. 120 mL samples of the system water were aseptically collected from the sample port located after the coupon rack at 2, 5, 10, and 30 minutes after the initiation of ozonation. Samples were refrigerated until they could be analyzed. Ozone concentrations within the system were determined for each sample collection.

After all samples had been collected, the ozone generator was turned off and the UV destruct was initiated. The system was run for 30 minutes or until the measured ozone concentration was below 40 ppb, the lowest possible measurement threshold for the ozone monitor. This residual ozone should not influence testing results, as lower measurements cannot be detected with accuracy. The system was then allowed to continuously recirculate process water.

After an initial rapid increase of the dissolved ozone concentration in the recirculating PW, the temporary concentration drop is caused when the automated ozonation system adjusts the ozone generator power to achieve its long-term setpoint. Any measurable ozone is quickly destroyed after turning off the generator and activating the UV destruct.

Each collected sample was analyzed as follows: dilutions of 10^{-1} through 10^{-6} were aseptically plated to TSA in duplicate. 1.0 mL, 10 mL, and 100 mL samples were aseptically filtered and rinsed using USP Fluid D, and the filters transferred to individual TSA plates. Plates were labeled with the sample time and dilution. All plates were incubated at 32.5 ± 2.5°C for 24 to 48 hours after which the colonies were counted and the CFU/mL for the system was determined for each sample time point. Using the CFU/mL at a given sample time and the initial challenge population, the log reduction in the system was determined for each time point.

After Challenge Test A, the water system was drained, refilled with DI water, and sanitized with ozone using the automated ozonation system. The system water was then verified as meeting USP Purified Water criteria per <1231> prior to commencing the next series of testing.

Challenge Test B: Adherent E. coli Biofilm Testing on Coupons

In Challenge Test B, four sequences of testing were conducted by varying the ozone setpoint concentration at 0 ppm, 0.5ppm, 2.0 ppm, and 5ppm. The effect of ozone on a biofilm of *E. coli*-inoculated on 316L stainless steel (SS) coupons was then measured at three different exposure time periods of 2 minutes, 5 minutes, and 10 minutes per concentration, totalling six coupons per concentration. The negative test without ozone (0 ppm) was run before the first ozonation sequence test to establish a comparative baseline for the experiment.

To ensure the destruction of any residual ozone in the time period between the concentration tests, the water system was allowed to run continuously with both the pump and the UV destruct on, ensuring both recirculating water flow and ozone destruction via the UV system. The ozone limit was confirmed to be < 40 ppb, the lowest possible measurement threshold for the ozone monitor. The production of USP Purified water also was confirmed before commencing each challenge test.

Inoculums for coupon testing were prepared as follows: a biofilm of *E. coli* was grown on a TSA plate and incubated at 32.5 ± 2.5°C for 48 hours. The plate was then harvested using a sterile hockey stick and PB water to prepare the inoculums stock. The inoculums stock population was verified by preparing dilutions in PB water and plating to TSA. The plates were incubated at 32.5 ± 2.5°C for 18 to 24 hours after which the colonies were counted and the stock population confirmed.

Sterile stainless steel coupons were aseptically inoculated with the *E. coli* inoculums described in the preceding paragraph to achieve at least 1 × 10^6 CFU/coupon upon recovery. The inoculums were spread on each coupon using a sterile glass hockey stick and allowed to dry for 15 to 30 minutes.

Inoculated coupons were aseptically transferred into separate covered sterile sample containers and stored covered until use.

Two positive control samples were prepared as above and retained for the determination of the challenge CFU/coupon. The challenge CFU/coupon was determined by first placing each control coupon into a sterile covered container with 100 mL of sterile PB water. The container with the coupon and PB water was then sonicated at 40 Hz for 10 minutes. Dilutions of 10^{-1} through 10^{-5} were prepared for each control coupon and plated to TSA plates which were incubated at 32.5 ± 2.5°C for 24 to 48 hours. Following incubation, the colonies on each control coupon were counted and the average CFU/coupon was determined for the challenge.

The positive control coupon acceptance criterion was the demonstration of at least 1.0×10^6 CFU/coupon of the challenge organism.

Baseline Test (Inoculated Coupons; Ozone Concentration at 0 ppm)

At the beginning of the Baseline Tests, two *E. coli*-inoculated coupons prepared as described above were placed into the coupon rack (Figure 2) using a wire mesh holder designed to keep the coupons vertical during the test. The coupon holder was then sealed and the system circulation initiated without ozone present in the system. After 2 minutes, the coupons were aseptically removed from the coupon rack and placed into 100 mL of PB water in a separate covered container labeled with the sample time point. This procedure was repeated with two new inoculated coupons with the only variation being that the coupons spent 5 minutes in the coupon rack exposed to the system water. This procedure was repeated a third time with an additional two new coupons and an exposure time of 10 minutes in the water system. All coupons were refrigerated immediately after collection. Each coupon was extracted by first sonicating the container, coupon and PB water for 10 minutes at 40 Hz, then preparing and plating dilutions of 10^{-1} through 10^{-5} in duplicate onto TSA. The plates were then incubated at 32.5 ± 2.5°C for 24 to 48 hours after which the colonies were counted and the average CFU/coupon determined. This analysis was repeated for each sample coupon. Using the average CFU/coupon and the initial challenge population as determined above, the average log reduction of the coupons was determined for each time point.

Ozone Tests (Inoculated Coupons; Ozone Concentrations at 0.5, 2.0, 5.0 ppm)

At the start of the first test sequence, an ozone concentration of 0.5 ppm was established in the circulation system. Once the system ozone concentration had stabilized at 0.5 ppm, the following procedure was used for test sequence #1:

1. Two inoculated coupons, prepared as described above, were aseptically placed into the coupon rack using a wire mesh holder designed to keep the coupons vertical during the test.
2. The coupon rack was sealed and the coupons exposed to the recirculating ozonated water for a period of 2 minutes.
3. At the end of this time, the coupons were aseptically removed from the coupon rack and placed into 100 mL of sterile PB water in a separate covered container labeled with the time point. The ozone concentration in the system at each sample time point was recorded.

Steps 1 through 3 were repeated in test sequences #2 and #3 which each employed fresh inoculated coupons and one difference in the procedure: for test sequence #2, the exposure time was 5 minutes; for test sequence #3, the exposure time was 10 minutes. All samples were refrigerated until they were extracted. The samples were extracted by first sonicating the coupon/PB water containers for 10 minutes at 40 Hz. Dilutions of 10^{-1} through 10^{-5} in duplicate were prepared and filtered for each coupon and transferred to TSA plates. The plates were then incubated at 32.5 ± 2.5°C for 24 to 48 hours, after which the colonies were counted and average CFU/coupon was determined. Using this value and the initial challenge population, the log reduction for the sample time point was calculated.

All three of the above test sequences and analyses were repeated using ozone concentrations of 2 and 5 ppm. Between each test sequence, the water system was drained, refilled, and ozone sanitized using the automated water ozonation system. The system water was verified as meeting USP Purified Water criteria per <1231> prior to commencing each test sequence.

Negative Coupon Controls (Non-inoculated coupons; not used in ozone system)

Negative coupon controls were prepared by placing a sterile SS coupon that had not been inoculated with E. coli in a sterile sample container with 100 mL of PB water. The coupon was then sonicated in the PB water container for 10 minutes at 40 Hz and then the entire 100 mL was aseptically filtered, rinsed with Fluid D and the filter transferred to a TSA plate. The plate was incubated at 32.5 ± 2.5°C with the test samples.

Log Tabulation

The microbiological test protocol was designed so that a series of dilutions would be plated to ensure countable plates. The lowest dilution plated from the coupon was 1:10. Therefore, if there was no growth on the plate, it would be reported as < 10 with a log value of 1. The log recovered would be subtracted from the challenge Log 6.4. Therefore, the sensitivity of the dilutions only allowed for total log reduction reporting of ≥ 5.4.

Recirculation Time	Ozone Concentration	Population Recovered
5 min	0 ppm	2.6×10^6 CFU/ml

Table A. Baseline for Challenge Test A: Population of *E. coli* in the USP PW storage and distribution system, following inoculation and prior to ozone treatment.

Exposure Time	Ozone Concentration		Log Reduction
	Ozone Generation System Exit	Test Skid	
2 min	0.825 ppm	0.17 ppm	0.0
5 min	1.651 ppm	0.73 ppm	0.0
10 min	1.790 ppm	1.56 ppm	1.0
30 min	2.112 ppm	0.31 ppm	6.0

Table B. Challenge Test A: Log reduction of planktonic *E. coli* at 2.6×10^6 CFU/mL in the USP PW storage and distribution system, using a 2 ppm ozone concentration setpoint.

Results and Discussion

E. coli was chosen to challenge the ozonated water sterilization protocol since it is a well understood microorganism that is known to colonize surfaces and which has been shown to produce biofilms on those surfaces.[18,19] As well, *E. coli* within a biofilm matrix have been shown to be resistant to disinfection using conventional chemical approaches, such as hypochlorous acid or monochloramine.[20]

As such, *E. coli* constitutes an excellent challenge species in determining the efficacy of ozonated water for the removal of biofilms.

At the beginning of each day of testing, positive control coupons were analyzed and the presence of *E. coli* contamination on the coupons' surface at a level of 2.6×10^6 CFU/coupon was experimentally verified. This verification was taken as confirmation that the coupons used in subsequent tests met the acceptance criterion.

The results of the planktonic *E. coli* challenge tests are shown in Tables A and B. The data in Table A clearly establish that the inoculum preparation and system loading procedures described above produced contaminant concentrations of planktonic *E. coli* in the pilot scale storage and distribution system that met the test acceptance criterion. The concentration of *E. coli* in the water system was determined to be 2.6×10^6 CFU/ml.

After the *E. coli* concentration baseline was established, the ozone generation began to achieve the 2 ppm setpoint. The following time measurements were taken from when the generator was first turned on, and includes the ramp up and stabilization of the ozone concentration in the complete water system.

Exposure Time	Ozone Concentration	Average Log Recovered	Log Reduction
2 min	0 ppm	4.4	2.0
5 min	0 ppm	4.3	2.1
10 min	0 ppm	4.2	2.2

Table C. Challenge Test B: Log reduction of *E. coli* on inoculated SS coupons at initial value 2.6×10^6 CFU/coupon. Ozone concentration in the circulating process water: 0 ppm (Baseline).

The negative control samples evaluated in this test sequence all proved satisfactory. The results of the planktonic challenge are presented in Table B and these data clearly show that a 30 minute ozone sterilization treatment of the inoculated pilot scale USP PW system using 2 ppm ozone concentration reduced the contaminant *E. coli* concentration by the desired 6.0 log reduction. The results of the tests evaluating the efficacy of ozonated water for the removal of *E. coli* and biofilms from stainless steel coupons are presented in Tables C through F.

Table C shows the results of the baseline tests with no ozone (0 ppm) present, where biofilm-inoculated SS coupons were placed in the coupon rack of the USP PW storage and distribution system and PW containing no ozone was circulated over the coupons at a flow rate of 12 gpm.

After exposure to PW at 0 ppm ozone concentration, the average log recovered value for all *E. coli* coupon contamination was 4.3. The average log reduction in surface contamination on these coupons for all test durations was thus 2.1. These results showed that, following an initial, rapid 2.0 log reduction in *E. coli* concentration during the first 2 minutes, the rate of *E. coli* loss from the coupon surface plateaued. It

Exposure Time	Ozone Concentration at Coupon Placement (ppm)		Ozone Concentration at Coupon Removal (ppm)		Total Log Reduction
	OGSI	PC	OGSI	PC	
2 min	0.472	0.54	0.486	0.55	4.9
5 min	0.480	0.58	0.470	0.58	≥ 5.4
10 min	0.491	0.58	0.498	0.59	≥ 5.4

OGSI – Ozone Generation System Input
PC – Post-Coupon measurement point
Note: Adjusted Log Reduction = Log Recovered (no ozone time point) – Log Recovered (ozone time point)

Table D. Challenge Test B: Log reduction of *E. coli* on inoculated SS coupons at initial value 2.6×10^6 CFU/coupon. Ozone concentration in the circulating process water: 0.5 ppm.

Exposure Time	Ozone Concentration at Coupon Placement (ppm)		Ozone Concentration at Coupon Removal (ppm)		Total Log Reduction
	OGSI	PC	OGSI	PC	
2 min	1.941	1.77	1.939	1.80	5.4
5 min	1.930	1.75	1.895	1.83	≥ 5.4
10 min	1.958	1.86	1.993	1.85	≥ 5.4
OGSI – Ozone Generation System Input PC – Post-Coupon measurement point					

Table E. Challenge Test B: Log reduction of *E. coli* on inoculated SS coupons at initial value 2.6×10^6 CFU/coupon. Ozone concentration in the circulating process water: 2.0 ppm.

Exposure Time	Ozone Concentration at Coupon Placement (ppm)		Ozone Concentration at Coupon Removal (ppm)		Total Log Reduction
	OGSI	PC	OGSI	PC	
2 min	5.215	4.92	4.909	4.75	≥ 5.4
5 min	4.636	4.81	4.912	5.01	≥ 5.4
10 min	4.912	4.92	4.782	4.92	≥ 5.4
OGSI – Ozone Generation System Input PC – Post-Coupon measurement point					

Table F. Challenge Test B: Log reduction of *E. coli* on inoculated SS coupons at initial value 2.6×10^6 CFU/coupon. Ozone concentration in the circulating process water: 5.0 ppm.

can be assumed that the sloughing of *E. coli* biofilm from the coupon surface was primarily due to water flow and pressure.

Following the baseline tests, tests for the efficacy of ozone exposure in removal of the *E. coli* and biofilms on the coupon surface were performed.

Table D shows the results from the first series of ozonated water tests in which the biofilm contaminated coupons were exposed to an ozone concentration of 0.5 ppm in the recirculating USP PW and subsequently analyzed for *E. coli* contamination. The results show that 2 minutes exposure to 0.5 ppm ozone in ultrapure water was insufficient to achieve the maximum decontamination, with the total log reduction after 2 minutes measured at a value of 4.9. After 5 minutes, the log reduction of *E. coli* reached a steady state value of ≥ 5.4 with no further reduction observed in the samples that were exposed to the ozonated water for 10 minutes. The baseline and 0.5 ppm ozone concentration tests were performed on the same day.

The results for sterilization tests performed at ozone concentrations of 2 ppm and 5 ppm were performed on the second day of testing and the results are shown in Tables E and F. The coupon challenge for these data indicated that while some of the challenge organism remained on the coupon surface after exposure for 2 minutes to 2 ppm ozonated water, after 5 minutes, no contamination was detectable. For coupons exposed to 5 ppm ozonated water, no contamination was detectable on any of the coupons at all the time points for exposure to the ozonated water. Note, the "≥ 5.4 log"= figure pertains to ozone removal alone, as shear-related biofilm removal has been subtracted out.

Conclusion

Ozone is increasingly used as both a sanitant and a sterilizing agent in pharmaceutical facilities. As a non-specific agent, the efficacy of ozone is related to the contact duration (time), method of action against the specific contaminant, ozone concentration, and water parameters such as temperature and conductivity.

In this study, a pilot USP PW production and delivery system using ozone sanitization was designed to represent typical large 316L stainless steel systems run at ambient temperatures in biopharmaceutical companies. Challenge Test A provided an overview of the time required to sanitize a contaminated system using ozone. Under these test conditions, in 30 minutes, ozone had achieved a 6-log sanitization (or sterilization). It is likely that using other methods to achieve an equivalent sanitation would likely require a longer time, with greater energy expended, plus significant additional minimum grade of USP PW water for system refill and flush to cleanse residuals from the system.

Challenge Test B demonstrated how ozonated water treatment can provide an effective means for biofilm removal and sterilization in UPW PW storage and circulation systems. The results indicate that ≥ 5 minutes exposure to ozonated water at concentrations of 0.5 ppm, 2.0 ppm, or 5.0 ppm ozone is sufficient to produce surface sterilization. The stainless steel coupons contaminated with 2.6×10^6 CFU/coupon of *E. coli* biofilm were sterilized under these conditions, with no challenge organism detectable following treatment with the ozonated water.

Through these experiments, ozone has proved to be highly and quickly effective against biofilm, at multiple concentrations and time points. It effectively sanitizes and sterilizes both contaminated water (planktonic biofilm) and contaminated surface biofilm. Ozone is shown to be effective in a matter of minutes, and in higher concentrations (e.g., "shock") it can impact biofilm even more quickly.

While multiple studies have demonstrated the overall effectiveness of ozone, the tests described above provide a quantifiable real-world simulation for a pharmaceutical facility. Additional studies can be conducted to simulate a larger PW system, and/or test the use of alternative materials

of construction (e.g., PVDF or other non-metallics) for the piping system. The use of a well-designed ozone system able to provide a steady, measurable, and adjustable ozone output concentration allows this technology to prove its effectiveness and ultimately its value in mitigating biofilms and other potential water system contaminants.

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Cleaning Validation: A Timely Solution for Improving Quality and Containing Cost

by Christopher Crone

This article presents an economic case for the use of on-line Total Organic Carbon (TOC) and conductivity analysis for validating automated CIP cycles with two separate case studies.

As the pharmaceutical manufacturing industry reacts to recent international legal decisions with respect to drug patent protection,[1] manufacturers continue to seek innovative ways to contain costs and maintain the quality associated with their brand. Globally, increased price pressure from generics will continue to force manufacturers to strive for increased production efficiency without increasing risk to pharmaceutical product quality. Reducing the overhead related to cleaning validation appears to be an attractive target for achieving cost containment goals. One manufacturer estimates more than 60% of equipment downtime is associated with cleaning.[2] While some instrument vendors currently recommend taking an at-line PAT approach for Total Organic Carbon (TOC) analysis,[2,3] this article argues pharmaceutical manufacturers can achieve further gains in efficiency by implementing a fully automated on-line cleaning validation program.

Many pharmaceutical manufacturers already enjoy some of the benefits of automation with Clean in Place (CIP) systems to ensure a consistent, validated cleaning method is applied to manufacturing equipment every cleaning cycle. And many of these same manufacturers are already using TOC for cleaning validation; in fact, a 2007 survey indicated that TOC was the most commonly used cleaning validation method among large molecule API manufacturers.[4]

Automation of cleaning cycles improves process control, reduces the risk of improperly cleaned manufacturing equipment, and offers significant cost savings over the life of a production line. However, verification of these same automated cleaning cycles is often done by manual grab sample collection, time consuming laboratory analysis, followed by labor intensive data review and reporting processes. Similar gains in quality and cost containment are realized when automated TOC and conductivity cleaning validation methods are integrated with the rest of the CIP process.

Verification of a cleaning cycle can easily take more than a day when manual processes are employed; much of this

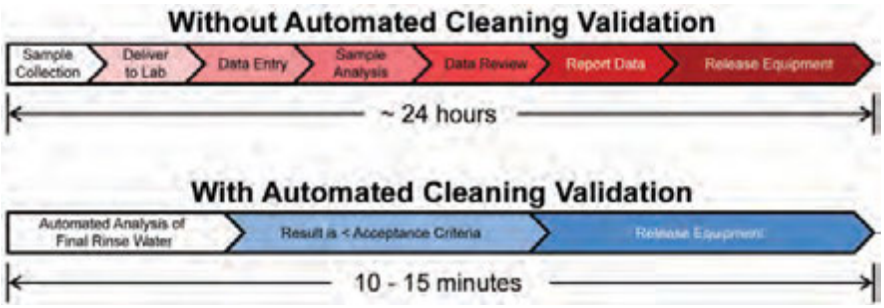

Figure 1. Comparison of workflow and equipment idle time or lost productivity with and without automated cleaning validation methods (on-line TOC and conductivity).

time is lost simply waiting for the next step in the process to occur. For example, imagine a sample of final rinse water is collected at the end of a cleaning cycle. Delivery of this sample to the QC lab might be delayed as the technician collecting the sample also must collect samples from other CIP cycles. Once the sample arrives in the QC lab, analysis may be delayed while the analyst prepares the instrument and enters data. Reporting of the data may be delayed until all the samples on the autosampler tray have been completed, and a supervisor has had the opportunity to review the data and quality control checks. These cumulative delays cause costly equipment idle time and reduce the productivity of manufacturing facilities. Figure 1 illustrates the workflow improvements and decrease in manufacturing equipment turn-around time that can be gained by adopting an automated cleaning validation approach.

Background

Cleaning validation is required per Code of Federal Regulations:

> 21 CFR 211.67 states *"Equipment and utensils shall be cleaned, maintained, and sanitized at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements."*[5]

Although the pharmaceutical manufacturing industry is anticipating publication of a new ISPE Cleaning Guide,[6] direction provided by the FDA's Validation of Cleaning Processes[7] indicates that rinse water sampling is an acceptable method of evaluating the cleanliness of systems that cannot be disassembled routinely. Furthermore, the FDA web page for Q&A on cGMP[8] states that Total Organic Carbon (TOC) is an acceptable method to use for cleaning validation.

FDA's PAT Guidance

According to the FDA's 2004 Guidance for Industry on Process Analytical Technology:[9]

- The Agency considers PAT to be a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality.
- The goal of PAT is to enhance understanding and control

the manufacturing process, which is consistent with our current drug quality system: *quality cannot be tested into products; it should be built-in or should* ***be*** *by design.*

The goal of continuous real-time quality assurance for processes such as cleaning is best achieved by automation and instrumentation. Some analytical verification methods more readily lend themselves to automation than others; for example, in-line conductivity measurement is one of the most commonly used cleaning verification techniques for final rinse water samples. This is because it is relatively easy to implement, gives fast results, and generates data which is easy to interpret. Conversely, a verification method, such as HPLC, does not readily lend itself to automation as implementation is more complicated, results typically take longer, and data interpretation requires some level of expertise.

Advances in TOC instrumentation also make this critical process parameter a good candidate for cleaning verification on automated CIP systems. TOC data is particularly useful for automated cleaning validation applications because sources of organic carbon contamination can include:

- Bulk water (purified water or water for injection)
- Active Pharmaceutical Ingredients (APIs), either small molecule or bio
- Cleaning agents
- Degradation products

The value of a specific method, such as HPLC, is limited because during a cleaning cycle, APIs can interact with cleaning agents to form unknown compounds, or may break down into unknown degradation products. These unknown degradation products may either be missed entirely on an HPLC method specific to the API, or if they are visible as peaks on the chromatogram, quantification is not possible. For these and other reasons, the Parenteral Drug Association cautions against using specific methods like HPLC in favor of non-specific methods like TOC and conductivity for cleaning validation.[10]

As with many enabling technologies, early adoption can provide a manufacturer with a competitive advantage; but as adoption rates increase over time, the technology becomes commonplace, those who are late to adopt lag behind at a competitive disadvantage. This is certain to be the case for automated TOC analysis on CIP systems. The business case for implementing automated TOC analysis is relatively easy to make.

If one considers lab consumables, a technician's time for collecting a final rinse water sample, an analyst's time for analysis of the sample, and laboratory data QC review, $65 per sample can be considered to be a conservative cost estimate per laboratory analysis. A medium sized manufacturing facility with multiple lines could easily expect to run 5000 CIP cycles per year. The cost of laboratory TOC analysis in this case would be $325,000 per year. Payback on the TOC automation project investment in this case can easily be achieved in the first year. Of course, this simple analysis only considers the costs associated with performing laboratory TOC testing; the most significant gains come from the increased productivity resulting from faster equipment turnaround. Estimates of financial benefit from productivity gains will vary widely depending on the value of the product being manufactured.

Instrument Selection

Bader, *et al*, correctly points out that a TOC analyzer should be selected based on instrumental characteristics and CIP process considerations.[11] One such consideration is whether or not an instrument requires continuous sample flow. Given the nature of automated CIP cycles, final rinse water is limited both in volume and time window available for sample collection. As such, a TOC analyzer selected for this application may be better suited for the intended purpose if its design employs a stop-flow analysis technique (batch process) rather than requiring continuous sample flow. TOC analyzers which require continuous sample flow may require special changes to a validated CIP process in order to accommodate the analyzer's continuous flow requirement. The need for continuous flow may be driven by a requirement to keep certain components such as membranes constantly wetted. Damage to the instrument could occur if the membrane were to dry out or if biofilm were to develop during stagnant conditions created by long periods of non-use.

Another consideration which should play an important role in TOC instrument selection is pH of the sample matrix. Because TOC analyzers oxidize organic carbon to CO2, and the solubility of CO_2 is greatly impacted by pH, a TOC analyzer that is calibrated with acidified organic carbon solutions may report erroneous values unless the sample is also acidified.

Much discussion has ensued regarding interference compounds when using direct conductivity TOC analyzers. While ionic conductive species may be present in trace amounts for final rinse water samples from CIP cycles, it should be noted that the presence of such species does not preclude TOC analysis methods such as direct conductivity from being fit for this application. According to USP 35 <1225> "Validation of Compendial Procedures," Linearity and Range:

> *"If linearity is not attainable, a nonlinear model may be used. The goal is to have a model, whether linear or nonlinear, that describes the concentration-response relationship."*

This implies that even if interference compounds are present in the sample matrix, demonstration of a repeatable and

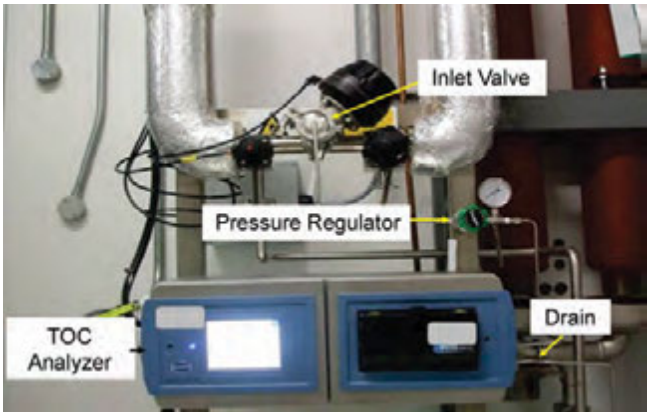

Figure 2. Automated on-line TOC analyzer installed for CIP verification.

proportional relationship between concentration and instrument response can be used to compensate for systematically elevated or suppressed instrument results. In practice, the concentration-response relationship is established during validation of the CIP skid, distributed control, and TOC analyzer as one integrated system. This argument is analogous to chromatography systems which routinely compensate for systematic errors during a calibration.

Goals for a Model Automated TOC Project

While each manufacturing facility will have goals specific to any individual automation project, some common themes will emerge across the industry. Among those include:

- Eliminating or reducing the requirement for manual sampling and subsequent QC analysis.
- Analysis of final rinse water demonstrates CIP cycle has achieved predetermined acceptance criteria.
- TOC analysis automation project is implemented with no or minimal change to existing CIP process (no impact to existing validated cycle).
- TOC analyzer is integrated with Distributed Control System (DCS), and provides automated response with a pass or fail result.

Implementation

The DCS on an existing CIP skid is programmed to receive information from the TOC analyzer. Modern TOC analyzers are capable of communication protocols, such as Modbus via TCP/IP; however, most automation engineers prefer to use the instrument's analog 4 to 20 mA output. The DCS also must be configured to send a start signal to the instrument's remote digital control circuit. An inline conductivity sensor is used for monitoring wash and rinse cycles prior to the final rinse, and verifies the final rinse water has achieved the predetermined conductivity acceptance criteria before initiating the automated TOC analysis. Empirically determined test data is needed to determine the lowest repeatable conductivity achievable.

Once communication is established between the TOC analyzer and DCS, and plumbing has been connected, CIP test runs are ready to begin. The analyzer determines TOC concentration by oxidizing organics with Ultraviolet (UV) light and measuring the carbon dioxide generated. After the user-configurable flush time elapses a sample is captured and held under stop-flow conditions. The Total Inorganic Carbon (TIC) concentration is determined before the UV lamp is turned on; once the lamp is turned on photolytic

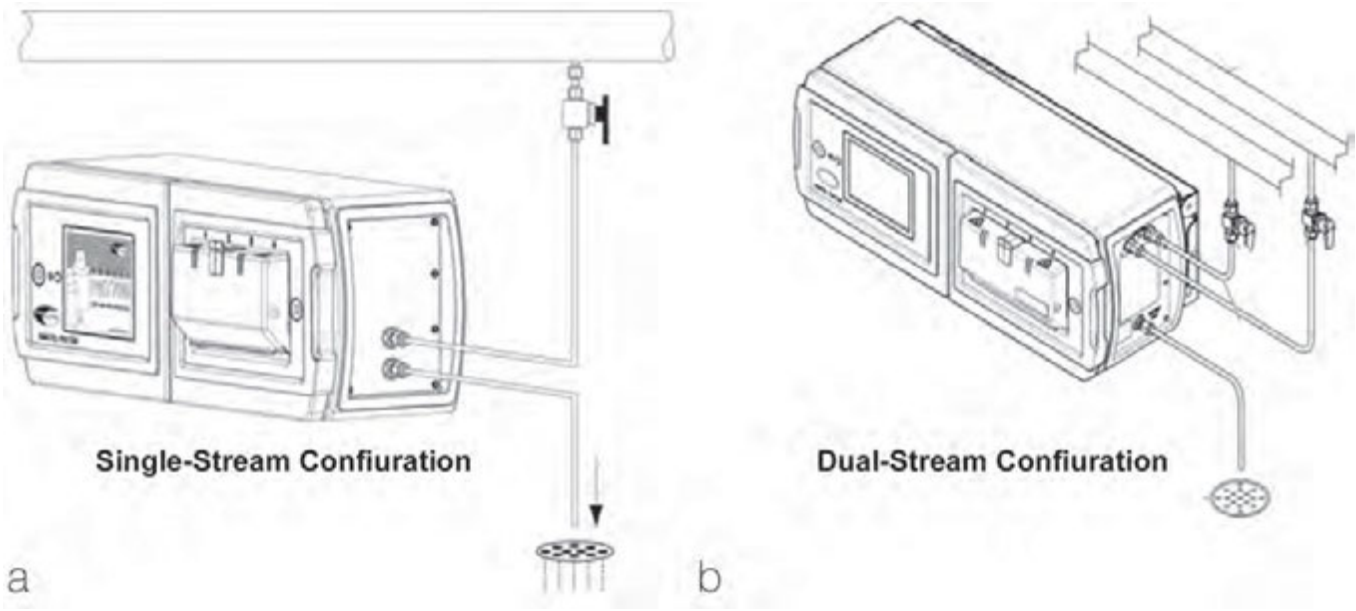

Figure 3. Illustration of automated TOC analyzer in both single-stream and dual-stream configurations.

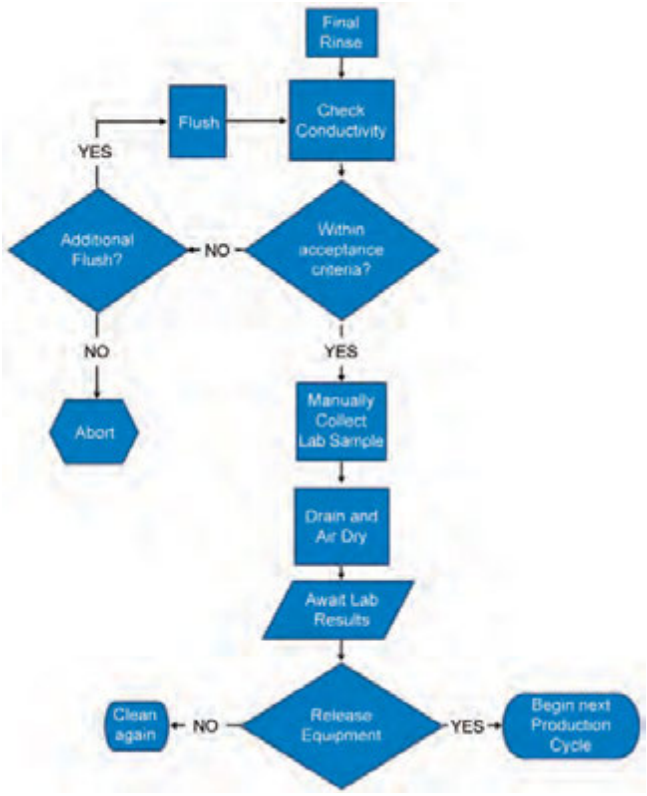

Figure 4. Model final rinse decision process without automated TOC.

oxidation of organic compounds is achieved with 185 nm UV radiation. Oxidation time varies with organic load; TOC concentrations below 100 µg/L (ppb) typically take less than five minutes, concentrations up to 500 ppb typically take six to eight minutes.

It is recommended to perform a TOC analysis of the water used for rinsing prior to analysis of the final rinse water in order to establish a baseline measurement. Establishing the rinse water baseline can eliminate rinse water as a source of contamination when a higher than expected TOC result is produced by a cleaning cycle. Measuring source water and final rinse water can be accomplished either by external valving or by using a TOC analyzer equipped with dual water inlets. TOC instruments with two water inlets are particularly attractive because they can be used to monitor PW or WFI most of the time, then be used for final rinse water analysis when needed. The dual-purpose approach helps to offset the cost of an instrument that would otherwise remain idle when cleaning cycles are not running. Figure 2 is a photo of an automated TOC analyzer installed for use in a CIP application. Figures 3a and 3b are illustrations of the single and dual stream configurations of the same TOC analyzer.

Figures 4 and 5 are flow charts of cleaning, verification, and production equipment release for manual sample collection and analysis as seen as Figure 4 versus automated as seen in Figure 5.

Steps in a CIP Cycle

1. **Pre-Rinse:** typically, tepid PW is used to loosen and remove bulk material from the surface of equipment. For bio-pharma cleaning applications, hot water may be undesirable due to potentially denaturing protein residues, which may in turn decrease solubility.
2. **Alkaline Detergent Wash:** an alkaline detergent wash commonly performs most of the cleaning during the cycle. Detergents are selected based on solubility, washability, and rinsability characteristics of both the pharmaceutical product being cleaned as well as the detergent itself. A one to two percent vol/vol concentration of a low-foam, highly rinsable product is commonly used.
3. **Rinse:** this step removes most of the alkaline detergent, usually with tepid PW. There is little value in determining the TOC concentration of the rinsate from this step as organic carbon from the alkaline wash will be present, and conductivity of this solution will remain relatively high.
4. **Acidic Detergent Wash:** this step neutralizes base from the alkaline detergent, and solubilizes residue which may have been insoluble in elevated pH solution from the previous wash. A one to two percent vol/vol concentration of a low-foam, highly rinsable product is commonly used.
5. **Rinse:** this step removes most of the acidic detergent and residue, again normally performed with tepid PW. As with the previous rinse step, there is little value in determining TOC for acidic rinsate.
6. **Final Rinse:** the final rinse step is usually done with hot

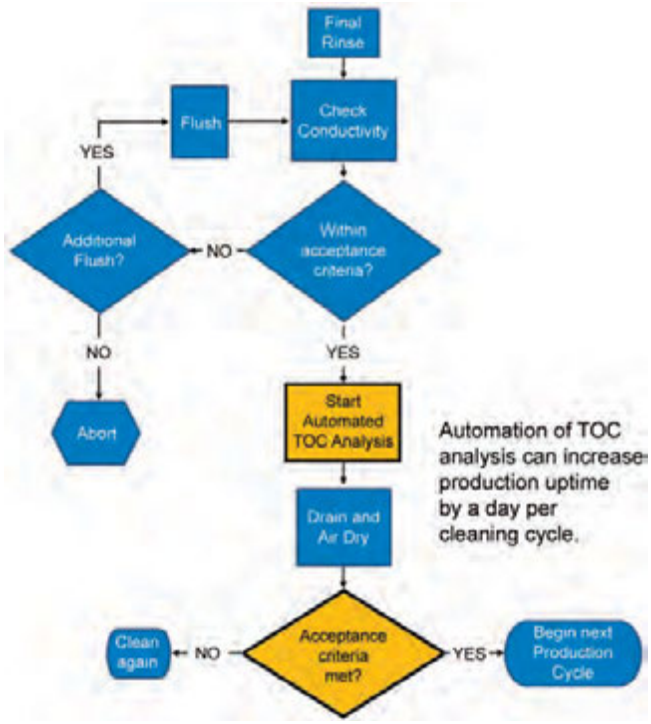

Figure 5. Model final rinse decision process with automated TOC.

	Sample 1	Sample 2	Sample 3	Sample 4	Sample 5
Cond (µS/cm)	1.03	0.95	0.85	0.69	0.70
Temp (°C)	18.5	18.8	17.2	14.6	16.9
TOC (ppb)	Over Limit	Over Limit	Over Limit	655	140

Table A. Conductivity, Temperature, and TOC results of five CIP process development runs.

	Pressure (bar g)	Duration (seconds)	Cond (µS/cm)	Temp (°C)	TOC (ppb)
Final Rinse Result	4.8	105	0.72	26.7	73

Table B. Results from final CIP process.

WFI, and removes the trace amounts of detergent and residues that may be left behind from the previous rinse. This is the last step before the process vessel is blown dry with hot air. After the final rinse step cleaned process equipment undergoes a documented visual inspection to verify a level of visual cleanliness has occurred. At this stage, swab sampling may be performed if necessary.

Case Study #1

Isopropanol was added to a 250 gallon test vessel to simulate organic residues from a bioreactor in order to first approximate rinse volumes and wash times. A differential conductivity TOC analyzer with a range of 1 to 1000 µg C/L was used. Reverse osmosis water was added in a stepwise manner while conductivity was monitored. Conductivity and TOC values exhibited a positive correlation – higher conductivity values predicted high TOC results. Table A shows the results of five analyses reporting uncompensated conductivity, temperature (°C), and TOC (ppb).

Next, a CIP process similar to Steps 1 to 6 outlined above was established for the bioreactor. Table B shows data from the final CIP batch report following the completed verification.

Case Study #1 Results: a CIP cycle with automated cleaning verification using TOC and conductivity was developed for use with each cleaning cycle. TOC and conductivity results are consistently below the acceptance criteria; production equipment idle time was reduced by approximately one day per batch.

Case Study #2

A validated CIP process similar to the steps outlined above had been in use for several years at a biopharma manu-

Trial Run Number	TOC (ppb)	Uncompensated Conductivity (µS/cm)	Temperature (°C)	Trial Run Number	TOC (ppb)	Uncompensated Conductivity (µS/cm)	Temperature (°C)
1	49.8	0.63	36.8	16	35.3	0.58	41.0
2	33.4	0.60	42.5	17	31.1	0.54	42.1
3	31.7	0.59	42.2	18	30.7	0.57	41.0
4	47.9	0.57	42.3	19	32.2	0.55	42.0
5	36.3	0.57	41.8	20	34	0.59	41.6
6	44.5	0.56	41.0	21	31.9	0.56	41.6
7	53.5	0.56	40.7	22	36.2	0.58	40.4
8	36.3	0.59	41.3	23	48.8	0.61	41.8
9	36.6	0.57	41.0	24	39.2	0.60	40.1
10	40.4	0.56	41.1	25	39.3	0.61	40.9
11	36.3	0.58	41.9	26	33.5	0.61	42.0
12	39.2	0.59	42.1	27	32	0.59	41.7
13	32.5	0.57	41.2	28	32.6	0.61	41.4
14	34.2	0.56	40.4	29	35.8	0.62	41.0
15	34.7	0.57	41.4	30	36.3	0.64	41.2

Table C. Results from online CIP evaluation.

facturing facility. The plant sought to expand the number of products produced at this facility, and identified cleaning validation as a critical production bottleneck. TOC and conductivity had already been in use for cleaning validation; however, the TOC analysis had been performed by QC Lab Technicians on manually collected grab samples. Due to the nature of the manual sample collection process, final rinse water samples were sometimes missed (human error). Technicians collecting final rinse water samples had been scalded by hot water more than once.

In addition to the automated TOC project goals stated above, this project also included the following goals:

- Eliminate the risk of missed samples
- Reduce health and safety risk to employees
- Increase manufacturing capacity to support new production of new API's not previously made at this facility

Thirty trial runs were conducted under varying conditions with multiple runs testing the cleanablity and reproducibility of results for each product made at the facility. A differential conductivity TOC analyzer with a range of 0.5 to 2000 µg C/L was used.

Case Study #2 Results: in all cases, the acceptance limits for both TOC and conductivity were met, and the online results yielded comparable results to laboratory analysis.

Conclusion

Although cleaning validation is required to ensure product quality and limit contamination risk, it is costly, time consuming, and often the primary obstacle to achieving greater manufacturing efficiency. Increasing competition from global generic drug manufacturers will continue to force pharmaceutical manufacturers to seek more efficient means of production. Manufacturers who have already embraced automated CIP processes have only realized partial gains if they have not also automated cleaning validation. Fear of the unknown is no longer a valid reason to postpone automating cleaning validation as more and more projects continue to gain regulatory approval. The time has come to accept the nearly decade old invitation from the FDA and apply PAT principles to cleaning processes, or be left behind by those who do.

Abbreviations

CIP	Clean In Place
FDA	Food and Drug Administration
µS/cm	micro Siemens per centimeter
nm	nanometer
ppb	Parts per Billion (µg/L)
PAT	Process Analytical Technology
PW	Purified Water
QC	Quality Control
TOC	Total Organic Carbon
UV	Ultra Violet
WFI	Water for Injection

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Steam Sterilization Principles

by Marcel Dion and Wayne Parker

This article presents how a good understanding of basic steam sterilization principles can help with avoiding most common mistakes made when using steam autoclaves.

Steam sterilization has been used for more than a century to sterilize items that can withstand moisture and high temperature. Steam is water in the vapor state; therefore, it is non-toxic, generally readily available, and relatively easy to control. A good understanding of basic steam sterilization principles and cycles is necessary to avoid mistakes that can lead to non-sterile load items, poor performance of the equipment, personnel injury, lower productivity, higher operation and maintenance costs, and damage to load items. Steam sterilizers are used for numerous applications in the pharmaceutical and medical device industries. The focus of this article is saturated steam applications, such as laboratory media sterilization, decontamination, and general component sterilization. Terminal sterilization of parenteral liquid products or devices containing liquids may require processes using steam-air mixtures or super-heated water-air mixtures. These processes, as well as in-situ sterilization of tanks, filters, etc., are not addressed in this article.

Steam Sterilization Principles

Six factors are particularly critical to assure successful steam sterilization:

1. Time
2. Temperature
3. Moisture
4. Direct steam contact
5. Air removal
6. Drying

1. Time

The exposure (sterilization) time is a critical factor simply because all the organisms do not die at the same time. A minimum amount of time at sterilization temperature is required to kill all the organisms. *Geobacillus stearothermophilus* (Bst) spores are generally used to test steam sterilizer cycles because they are extremely resistant to moist heat sterilization. They are also non-pathogenic and commercially readily available. The number of survivors is usually plotted on a logarithmic scale. A straight line survivor curve such as the one shown in Figure 1 is typical.

The D-value (time to reduce the microbial population by 90%) for Bst should be 1.5 to 3.0 minutes at 121.1°C (250°F) .[1] For the purpose of this discussion, a D_{121} value of 2.0 minutes and a sterilization temperature of 121°C (250°F) is used. A typical sterilization cycle will include an exposure phase of at least 20 minutes at 121°C (250°F) for a Sterility Assurance

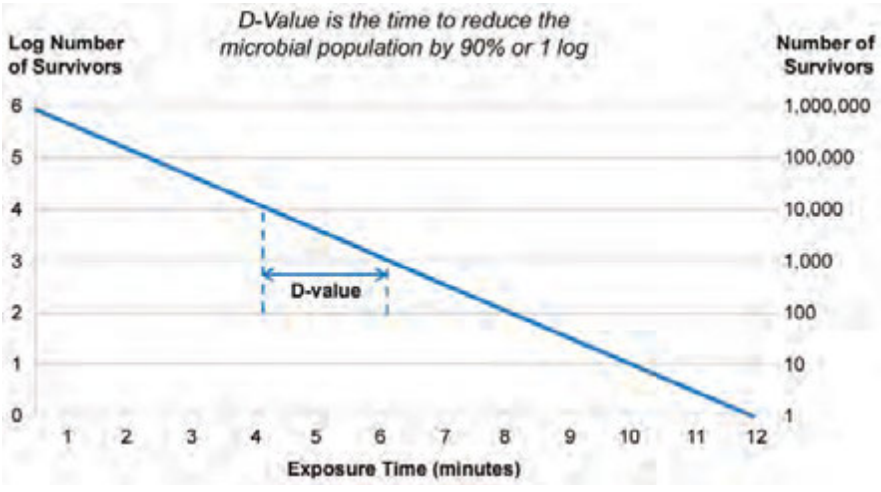

Figure 1. Typical survivor curve.

Level (SAL) of 10^{-4}, assuming a starting population of one million (10^6) organisms. This means there is a one in ten thousand (10^{-4}) chance of a single viable Bst spore surviving the process. For each additional two minutes of exposure at 121°C (250°F), the SAL is decreased by a factor of ten. The required SAL varies with application. Care should be taken to assure the correct SAL is targeted prior to cycle development. The actual bioburden of the products being sterilized will logically be killed faster than Bst. The resultant "overkill" is an accepted method for sterilization of durable items and should be used when possible.[2]

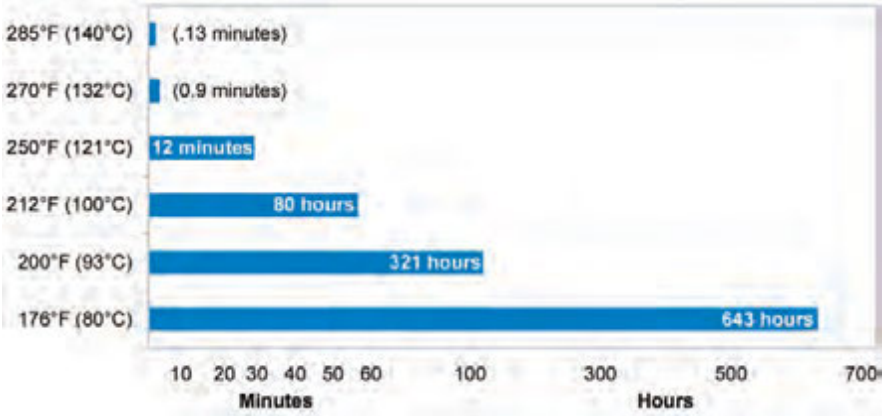

Figure 2. Sterilization time versus temperature.

2. Temperature

The second critical factor in steam sterilization is the temperature of the saturated steam controlled in the chamber of the sterilizer. Figure 2 clearly demonstrates how increasing the temperature dramatically reduces the time needed to achieve sterilization. Figure 2 illustrates approximately how much time is required to achieve equivalent microbial lethality (SAL 10^0 with a starting population of 10^6, D_{121}- value 2.0 minutes) at different moist heat exposure temperatures.[3] The temperature of saturated steam is directly related to the pressure at which it is controlled. The pressure-temperature relationship values are shown in saturated steam tables.[4] A typical cycle at 121°C (250°F) will require 15 to 17 lbs of gauge pressure (103 to 117 kPa) in the chamber of the sterilizer. The gauge pressure required will be higher than the pressure shown in the saturated steam table due to air mixed with the steam and elevation above sea level. The maximum pressure in an autoclave is limited by the specifications (ASME pressure rating) of the pressure vessel (chamber and jacket).

3. Moisture

Moisture in the steam has a major impact on its ability to denature, or coagulate proteins; hence the importance of using saturated steam. Saturated steam is at equilibrium with heated water at the same pressure, which means it contains the maximum amount of moisture without liquid condensate present. Saturated steam is recommended for steam sterilization. Not all steam is acceptable for use in a sterilizer. A dedicated clean steam supply is recommended. Superheated steam, steam containing excessive liquid water, and steam containing excessive boiler additives or contaminates (such as rust) should be avoided. Superheated steam is defined as steam that is above its saturation temperature. Superheat occurs in steam distribution systems when the line pressure is dropped across a Pressure Reducing Valve (PRV). The larger the pressure drop, the more superheat is created. Superheated steam does not contain the required moisture necessary to assure sterilization. The excess energy in superheated steam is transient and is eventually dissipated by the items in the sterilizer chamber, but can cause difficulty when validating the sterilizer to the empty chamber temperature stabilization requirements of the European Standard EN285.[5] The ideal clean steam system for steam sterilizers is regulated at 30 to 35 psig (207 to 241 kPa) at the source. EN285 indicates the steam supply pressure should not be more than twice the chamber pressure at the desired temperature. Superheat is also created when saturated steam passes over a surface at a higher temperature. The sterilizer jacket temperature should always be set slightly below the chamber sterilization temperature to avoid superheating of the steam as it enters the chamber.

4. Direct Steam Contact

Direct steam contact with the surface of the object to be sterilized is required for the steam to transfer its stored energy to the object. Without direct steam contact to all surfaces, the item will not be sterilized. The amount of energy stored in steam is much higher than dry air or water at the same temperature. From the saturated steam table mentioned above, one can see that it takes 419 kJ/kg (180 Btu/lb) to heat water from 0°C to 100°C (32°F to 212°F). This is the enthalpy of water (hl). It takes an additional 2,257 kJ/kg (970 Btu/lb) to create steam at atmospheric pressure (100°C or 212°F). This additional energy stored in the steam is the enthalpy of vaporization (he), and is the key to steam sterilization. In order for the steam to transfer its stored energy, it must condense on the surface of the object being sterilized.

5. Air Removal

Air is the biggest deterrent to steam sterilization. Air must be removed from the chamber and the load before direct steam contact and sterilization can occur. This is accomplished in a steam sterilizer by a series of vacuum pulses prior to sterilization (pre-conditioning phase). A small amount of air will


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always be present in the autoclave chamber, but must be minimized. Insufficient air removal, sterilizer chamber vacuum leaks and poor steam quality (excess non-condensable gases) are the most common causes of sterilization failures.

6. Drying

Wrapped items must be dry before they can be aseptically removed from the sterilizer. Condensation is the natural result of steam contact with the cooler surfaces of the load during the heating and exposure phases. The presence of condensation (wet packs or pouches) can cause re-contamination of the load when removed from the sterilizer. A steam sterilizer dries the load after sterilization by drawing a deep vacuum in the chamber (post- conditioning phase). A vacuum level of 1.0 to 2.0 psia (6.9 to 13.8 kPa) is recommended for efficient drying. At 1.0 psia (6.9 kPa) chamber pressure, water boils at 38.7°C (101.7°F). Therefore, the condensate will boil and be removed as steam through the sterilizer's vacuum system. The energy required to boil the condensate comes from the load itself. As the temperature of the load cools due to evaporation of the condensate, evaporation (drying) decreases. When the load temperature cools to the boiling point of water at the drying vacuum level, drying is negligible. Adding further drying time past this point will not provide any further drying. Optimal load drying times depend primarily on load density and packaging. Due to their low density, plastic and rubber items may require additional drying, as they cool rapidly (pulsed air or heated pulsed air drying post-conditioning processes). The amount of residual moisture in a package can be determined by weighing the package before and after the sterilization process. Typically, verification of the absence of visible water droplets on or in the package is sufficient.

Steam Sterilization Basic Cycles

Steam sterilization cycles typically consist of three phases:

1. Pre-Conditioning: during this phase, air is removed from the chamber and the load is humidified by means of alternating vacuum and pressure pulses.
2. Exposure: during this phase, the chamber temperature is raised to and held at the programmed sterilizing temperature for the programmed exposure time (both are user selectable). The exposure also may be controlled by accumulated F_o for liquids if a load probe and appropriate sterilizer controls are used. Refer to point #7 in common mistakes section below for more information on F_o.
3. Post-Conditioning: during this phase, dry goods loads are cooled and dried or a liquids load is cooled. The chamber pressure is brought to atmospheric.

Over the years, various cycles have been developed for different applications. It is critical that the proper cycles be used.

- A basic **gravity cycle** (cycle without pre-vacuum) can be used for items such as unwrapped metal components, glassware, or non-porous items that do not entrap air.
- **Liquids** require modified gravity cycles to prevent liquid loss from boiling over. Liquids in open or vented containers or in bottles with loose caps can be processed in a "basic" liquid cycle (with slow exhaust). The cooling (exhaust) phase of this cycle allows for the chamber to **slowly** return to atmospheric pressure to prevent boil-over as seen in Figure 3. Nominal liquid loss due to evaporation during the slow exhaust phase is typically 10 to 15%. The time required for the slow exhaust phase can vary considerably depending on the volume of liquid per container and per load. Larger volumes require slower exhaust rates. Use of a load probe and F0 exposure control is recommended. **Vented containers only are to be used with this process.**

Liquids are at or near boiling temperature at the end of a slow exhaust cycle and must be allowed to cool before the load can be safely removed from the sterilizer. Liquids in sealed containers require an air overpressure cooling cycle to prevent explosion of the container(s) during the cooling phase or unloading process as seen in Figure 3. Clean, dry compressed air (process air) is admitted to the sterilizer chamber at the end of the exposure phase and controlled at a pressure higher than the pressure of saturated steam at the temperature of the load probe. As the air flows over the load, the load is cooled and the chamber pressure starts to drop due to condensa-

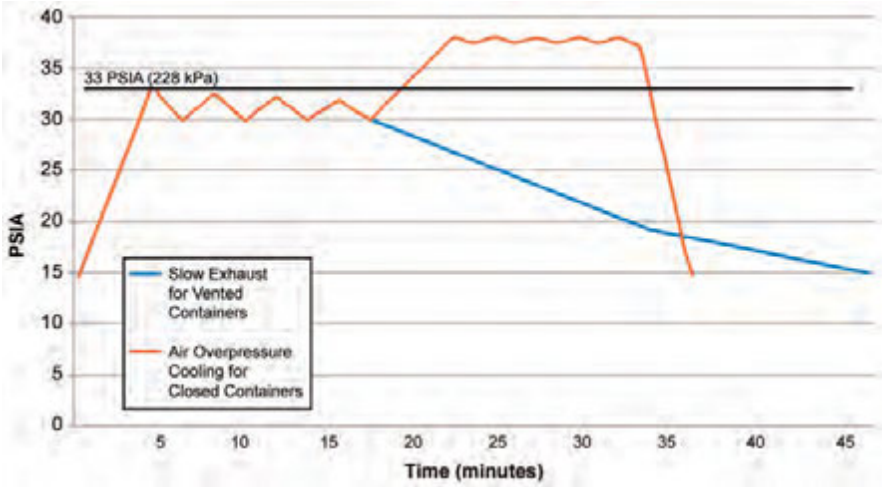

Figure 3. Typical liquid cycle chamber pressure at 121°C (250°F).

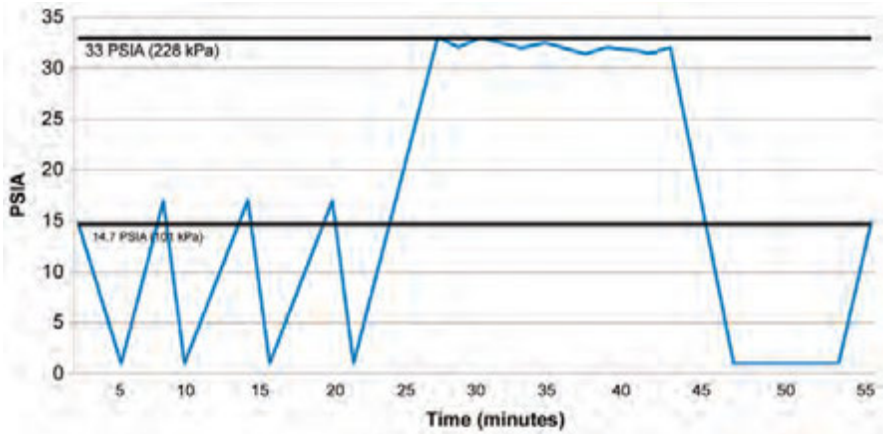

Figure 4. Typical prevacuum cycle chamber pressure at 121°C (250°F).

tion of steam in the chamber. The supplied compressed air flow rate must be sufficient to maintain overpressure during the entire cooling phase. This "Air Cooling" process is highly recommended for sterilization of liquids in sealed OR vented containers because it eliminates evaporation and boil-over during the cooling phase. In addition, liquids can be cooled to a temperature safe for handling (60°C to 80°C (140°F to 176°F)) during the process by flowing water through the sterilizer jacket during the cooling phase. The load can be safely removed immediately upon cycle completion. The American Society of Mechanical Engineers (ASME) pressure rating of the sterilizer limits the amount of overpressure than can be utilized. Fill volume has a significant effect on the internal pressure of the sealed container. The lower the fill volume, the lower the internal pressure will be due to compression of the air in the head space of the container. The approximate internal pressure of a sealed container can be calculated using Robert Beck's equation.[6]

- Since air is generally a deterrent to sterilization, a "**Prevacuum**" cycle (alternating vacuum and pressure preconditioning pulses) is recommended for all loads other than liquids (Figure 4).

Measuring Performance

Several methods can be used to verify the efficacy of the sterilization process. Typical methods use Biological Indicators (BIs) and Chemical Indicators (CIs) that are placed in worst case positions in the load and/or in test packs.

- **Biological indicators** provide the best test for sterilization and are used to establish the efficacy of the cycle. In this category, we can find:
  - Inoculated spore test strips. The strips must be aseptically transferred to an incubated growth media soon after the sterilization process is complete.
  - Self-Contained Biological Indicators (SCBI) (Figure 5). Because they are self-contained, SCBI's reduce chances for false positives due to poor aseptic transfer technique. They are typically used to monitor the effectiveness of steam sterilizing process.
  - Glass ampoules are also used when the indicators must be placed in a liquid product to be sterilized (culture media as an example).
- **Chemical indicators** provide immediate proof of steam penetration (not necessarily of sterilization). In this category, we can find:
  - Autoclave tapes that show the process has occurred with no correlation to time/temperature.
  - Chemical integrators that are correlated to time and temperature. These particular indicators can help reduce cycle development time by providing immediate indication of sterilization efficacy.
  - **Steam penetration studies:** temperature sensors can be placed in hard to reach locations to provide indication of steam penetration.

Prevacuum sterilizers should be tested routinely for air leaks and air removal capability. Automatic chamber leak tests (vacuum hold tests) are typically provided in the software of modern prevacuum sterilizers, and should be run daily after a warm-up cycle. The sterilizer chamber is evacuated to the limit of the vacuum system (<1.0 psia or 6.9 kPa) and the chamber and associated piping are isolated (valves closed) for a hold period. The difference between the absolute pressure at the beginning and end of the hold period is the total leak rate. The leak rate should be < 1.0 mm (0.039 inches) Hg/minute[(2)]. Hold time varies per procedures, from 10 to 30 minutes. It should be noted that a pressure rise during the hold phase is not always indicative of a chamber vacuum leak.

Figure 5. Self-Contained Biological Indicators (SCBI).

Wet steam can cause condensate to be introduced into the chamber during the test preconditioning pressure pulses. Any condensate in the chamber will evaporate at the test vacuum level, causing a rise in chamber pressure. One practical way to determine the source of the pressure rise is to observe the leak rate during the vacuum hold phase with an absolute pressure gauge connected to the sterilizer chamber. An air leak rate will be fairly constant over the vacuum hold period. A pressure rise from evaporation of condensate will result in a high rate at first, and then will diminish as the condensate is evaporated.

In addition to the vacuum hold test, a challenge test such as the Bowie-Dick test should be run periodically as seen in Figure 6. The challenge test is different from a vacuum hold test in that it challenges the sterilizer to remove the air from within a dense package and displace the air with steam. It is fairly uncommon for a sterilizer to pass a vacuum hold test and fail a challenge test, but it has been observed. Insufficient air removal during the prevacuum phases and/or poor steam quality (excess entrained non-condensable gases, superheated steam or wet steam) can cause this anomaly. Challenge tests are temperature specific, and tests designed for 132°C (270°F) will not function properly in a 121°C (250°F) test cycle.

The Ten Most Common Mistakes in Steam Sterilization

Most mistakes regarding the programming and operation of typical steam sterilizers are related to the basic principles of steam sterilization.

1. Containers with closed valves, empty glass bottles with tightened screw caps or secured aluminum foil are placed in the sterilizer.

As a result, steam cannot directly contact the inside surfaces and sterilization does not occur. This problem can be resolved by assuring that all items in the sterilizer have a way for the steam to get in and the air to get out. If there is uncertainty about whether an item's configuration, set-up, packaging, or orientation will allow adequate steam penetration, a thermocouple, chemical and/or biological indicator can be placed inside the item to be certain.

2. Pouched and/or heavily wrapped items are tightly packed in the chamber.

As a result, air may remain trapped in the items after the preconditioning phase and prevent sterilization. Items should not be overwrapped, and sufficient space should be maintained between load items. The preconditioning vacuum and pressure pulses must be set correctly to attain complete air removal from the load. Typically, four (or more) preconditioning vacuum pulses should be programmed to reach at least 28 in (711 mm) Hg vacuum ((1.0 psia or 6.9 kPa (absolute)) to assure sufficient air removal for worst case loads. Some very dense loads may require a short (2 to 5 min) hold phase at peak preconditioning vacuum to allow time for trapped air to be removed. Preconditioning pressure pulses should be programmed for 3 to 5 psig ((21 to 34.5 kPa (gauge)). Higher pressures set for prevacuum pressure pulses can result in an excessive amount of superheat and difficulties with temperature stabilization during the first few minutes of the exposure phase.

Figure 6. Bowie-Dick test pack.

3. Heavier items are placed on top shelves.

Water droplets and/or stains are observed on the outside of wrappers of items placed on the mid to lower shelves after the sterilization cycle is complete. Because the items are not dry, they cannot be aseptically removed from the sterilizer. Condensation is the natural result of steam contact with the cooler surfaces of the load. The condensate will fall from shelf to shelf. The denser the load item, the more condensate is created. Therefore, place heavier items on the bottom shelf. In addition, consider placing a cotton sheet or lint free towels on each sterilizer loading cart shelf prior to loading to allow the condensate to be absorbed. This also aids in drying. As the condensate wicks into the sheet or lint free towels, the condensate surface area is greatly increased and evaporates much more rapidly during the drying phase than the same amount of condensate in a droplet or a puddle.

4. Load is too dense or items are positioned incorrectly in the load.

As a result, wet or damp items are observed at the end of the cycle. Wrapped items positioned so that condensate is allowed to collect will not be dried. Items should be positioned so that the condensate is allowed to flow downward. Items (wrappers, pouches, filters, or other porous biological barriers) that remain wet at the end of cycle cannot prevent contamination of the load when removed from the sterilizer. As the load cools outside the sterilizer, the water in the wrapper will be drawn into the wrapped item. Any contamination that is present in the environment can be drawn through the sterile barrier along with the water. There are numerous other possible causes for wet loads. The most common are:

a. Insufficient drying vacuum level or time programmed
b. Rubber or plastic items in pouches (i.e., rubber stoppers, plastic tubing) may require additional drying (a pulsed-air or heated pulsed-air drying process is recommended for these items)

c. Wet steam

While there is no single solution to eliminating wet loads, it's likely that experimenting with drying time, repositioning items, reducing load density, modifying cycle settings, and investigating steam quality will resolve the problem.

5. Pouches are placed flat on the sterilizer shelves or stacked on top of one another.

As a result, pouches may have water droplets inside and cannot be aseptically removed from the sterilizer. Typical cause is when the condensate naturally created when steam penetrates the pouch and contacts the surface of the item within is not removed during the post-conditioning drying phase. Pouches should be spaced properly and placed in rack that holds the pouch on its edge (Figure 7) to prevent pooling of the condensate inside the pouch. Pouches should not be placed flat on the sterilizer shelf. Pouches should not be overloaded. Remember that more mass means more condensate.

Sufficient drying vacuum level and time should be programmed to allow for complete evaporation of the condensate. Wet steam should be corrected. Double pouching may require additional prevacuum pulses with dwell time at maximum vacuum and increased drying time. Doubled pouches should never be assembled so that the items inside cannot be seen. Pouch flaps should not be folded over.

6. Liquids in vented containers are placed in a deep pan to catch boil-over (slow exhaust cycle).

The pan will hold water and it will hold air. The steam cannot contact the surfaces within the pan because of the trapped air, and they will not be sterilized. The solution is to eliminate the pan and adjust the sterilizer slow exhaust rate to prevent boil-over. A shallow pan, less than 1" (25 mm) deep, can be used in the event that a small amount of boil-over cannot be eliminated by adjusting the slow exhaust rate.

7. "Overcooked" Media

Over sterilization of media will caramelize the sugars and render the media useless. The typical overkill approach is not recommended for sterilization of media. The exposure phase should be programmed to achieve the desired SAL and no longer. Use of a load probe and F0 exposure control is recommended for sterilization of media in containers larger than 100 ml (3.4 oz). As illustrated in Figure 8, F0 is a calculation of the equivalent exposure at temperatures other than 121.1°C (250°F). As the liquid is heated, the calculated F0 (from the load probe temperature) is accumulated until the selected F0 exposure value (minutes) is achieved, at which point the cycle proceeds to the exhaust/cooling phase. For example, on the graph, the kill rate on the same population of organisms is half as effective at 118°C (245°F) as at 121°C (250°F). Therefore, at 118°C (245°F), it will require twice the exposure time

Figure 7. Proper position for pouches.

to kill the same number organisms.

A common formula for calculating the F_0 value is:

$$F0 = \int_0^t L\,dt \quad \text{where} \quad L = 10^{\frac{(T-121.1)}{z}}$$

where:

- L is lethal rate of bacterial spores
- t is exposure time, [s]
- T is exposure temperature, [°C]
- z is a constant, [°C]

The constant z describes the slope of the thermal death curve. The widely accepted value for z is 10°C (18°F) in steam sterilization.

8. Using cold water for vacuum pump that is too hot.

As a result, the vacuum pump may not be able to reach 1.0 psia (6.9 kPa). The heart of the prevacuum sterilizer is the water-ring vacuum pump. The efficiency and maximum vacuum capability of a water-ring vacuum pump are adversely affected by higher water temperatures typically encountered during the summer months. During operation, the water within the pump is heated by mechanical friction and heat energy from the sterilizer chamber. If the temperature of the water inside the pump reaches 39°C (102°F) during the preconditioning

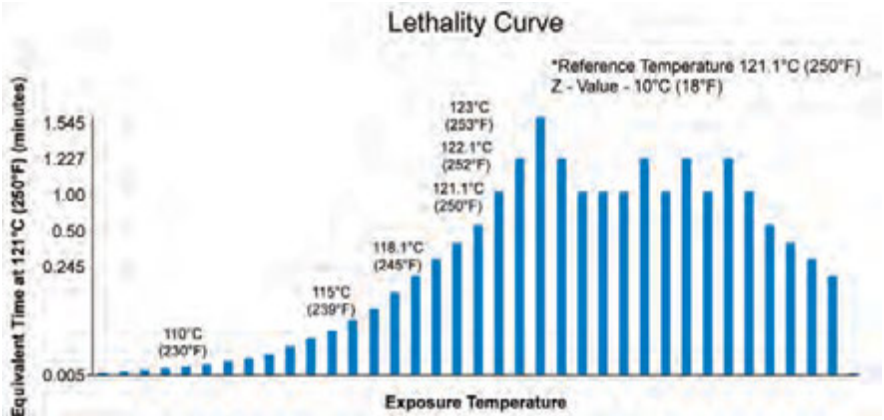

Figure 8. F_0 as a function of temperature.

or post conditioning vacuum peak, the water inside the pump will boil at ≤ 1.0 psia (6.9 kPa) and cause cavitation. In this case, the recommended preconditioning vacuum level of 1.0 psia (6.9 kPa) cannot be achieved in the sterilizer chamber. A common "work-around" for this situation is to change the set point of the prevacuum pulses to a level that can be achieved. Insufficient air removal can be the result unless the number of vacuum pulses is increased, causing longer cycle times and less effective air removal. Internal pump temperatures higher than 39°C (102°F) are often observed during the summer months if the water supplied to the pump is not cooled. Chilled water is ideal, but typically too expensive to use in a sterilizer vacuum pump arrangement in which the water flows from the vacuum pump to drain. The recommended solution is a recirculation/cooling system for the vacuum pump water that uses chilled water in a closed loop heat exchanger. This configuration is eco-friendly as it saves a significant amount of water. In addition, the vacuum pump efficiency is not subject to seasonal water temperature fluctuations.

9. Load probe is available, but not used.

Most modern sterilizers include (optional) an RTD load probe and F_0 exposure control for use in liquids sterilization, but many times the probe is not used. If equipped with a load probe, the exposure can be controlled by the temperature of the liquid rather than the temperature in the drain line. Without the load probe, the temperature of the liquid is not known and can only be estimated, resulting in inadequate (non-sterile) or excessive F_0 (overcooked). The load probe should be placed in a container of water approximating the volume of the largest volume of liquid being sterilized. Load probe control/F_0 must then be selected in the sterilizer control settings.

10. Pressure/vacuum rate control is available, but not used.

Most modern sterilizers include (optional) rate control for the vacuum and pressure ramps, but many times the rate control is not used. When no pressure rate control is applied steam will enter the chamber at maximum velocity during the preconditioning pressure pulses, which creates a superheat problem and EN285 compliance problems as discussed earlier. Slowing the pressure rate allows time for superheat to dissipate during the ramp up.

When no vacuum rate control is applied the chamber will depressurize at the maximum rate of the vacuum pump. The typical problem associated with this is burst pouches. Slowing the vacuum rate allows time for the pouch internal pressure to equilibrate and prevents bursting during the preconditioning and post conditioning vacuum phases.

Conclusion

Steam sterilization is a process that is dependent on basic principles that are sometimes unknown or disregarded by the sterilizer user. A large percentage of steam sterilizer failures can be solved by logical and practical application of these basic principles. It should be noted that proper training for sterilizer users should include this education. Proper wrapping and loading techniques are critical for safe and successful sterilization. As with any critical process equipment, proper maintenance and calibration is essential.

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Comparing Energy Consumption of RABS and Isolator Configurations

by Benjamin Hoffman, Katarzyna Frank, and Johannes Rauschnabel

This article presents a comparison of energy consumption of the ventilation and air conditioning system for a passive RABS, an active RABS, and an isolator system, including the different clean room requirements.

While cost reduction is a major driver for the healthcare industry, it should not affect quality improvements in pharmaceutical manufacturing processes. Patient safety must remain the first priority. This is why aseptic manufacturing of parenterals is increasing wherever possible. This trend is supported by growing experience and many innovations in barrier systems, such as Restricted Access Barrier Systems (RABS) and isolators. To meet the economic requirements of the future (and thereby cost control), energy consumption of manufacturing systems will increasingly become a major focus.

This article will provide a detailed comparison of energy consumption for a clean room, a RABS and an isolator installation of a parenteral fill/finish line in a green field approach. The calculation will take into account all energy sources like chilled water, hot water, steam and electrical power, as well as the energy consumption for ventilation and conditioning of the corresponding room concepts. The comparison is based on VDI 2067 Part 21 2003-05.[1] It does not result in cost estimates, as costs may differ significantly depending on location, climate and energy price discounts.

Each installation must, of course, be evaluated individually; however, this article offers an approach on how to integrate energy consumption into investment decisions.

Technical Building Services

Air conditioning in technical building services is a key factor for a engery-efficient production, especially in the pharmaceutical industry. Depending on production conditions, barrier systems and different air conditioning systems can be applied. Air handling systems control temperature and humidity and the numbers of particles and germs by means of filtration. It is also possible to achieve different pressure levels among the clean rooms and pressure differences between clean room, and for example, a filling line. By managing the differential pressure, the transportation of particles, viables or contaminated air into the process environment can be specifically controlled. This article will focus on the most frequently used systems: central recirculation/mixed air conditioning and local mixed air systems with central outside air conditioning as seen in Figure 1. These systems conform to the principle setup of barrier systems according to ISPE Good Practice Guide.[2] In addition to those mentioned, the pharmaceutical industry also uses straight outside air systems and recirculation air systems.[3]

Central Recirculation/Mixed Air Conditioning System

A central recirculation/mixed air conditioning system is equipped with a common central air handling unit for all clean rooms. The supply air and recirculation air passes through all components of the air handling unit, which consists of the following components: mixing chamber, filter, heater, cooler and humidifier. The cooler chills and dehumid-

ifies the air. Depending on customer requirements, the air can optionally be dried by a desiccant rotor instead of a cooler. In this system, the pressure levels of the different rooms are obtained by air flow control valves and the temperatures by heaters. The exhaust air of all rooms is brought together. The majority is used as recirculation air and is mixed with outside air before being handled again. The air exchange between the rooms might cause a risk of cross-contamination for product groups with differing requirements. The central recirculation/mixed air conditioning system is used for the supply of just one production area (single production line). It is not commonly used for a joint supply of different production areas. Variations of this ventilation concept are also frequently applied, for instance, by using a heat recovery system instead of the mixing chamber with optional evaporative cooling of the outgoing air.

Local Mixed Air System with Central Outside Air Conditioning

A local mixed air system with central outside air conditioning is preferably chosen when different rooms have to be controlled individually. Each room is equipped with an individual local air handling unit for the recirculation air. This unit features a cooler, filter and humidifier, enabling temperature and humidity of the supply air to be controlled individually for each room and independently from internal thermal loads or humidity loads of the rooms. The local mixed air system with central outside air conditioning can be optionally equipped with a heat recovery system as seen in Figure 1.

The portion of fresh air required to increase the level of oxygen for the rooms or to compensate air loss through leakages is supplied by the central outside air conditioning. The outside air flow rate, for instance, equals 20% of the total amount of recirculation air volume of the rooms. The supply air passes the entire local mixed air system. The exhaust air flows of the individual rooms are brought together and are dispensed to the surroundings via a heat recovery system. There is no risk of cross-contamination, because the supply air to the rooms is purified by fresh outside air, without adding exhaust air.

Clean Room

Clean rooms are subject to strict and standardized purity specifications. The maximum allowable numbers of particles per volume of air are defined in ISO 14644-1. Pharmaceutical clean room environments refer to that standard, and regulations specify the cleanliness grade for specific production situations – including criteria for viable particles and germs.

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PARTICLE MEASURING SYSTEMS

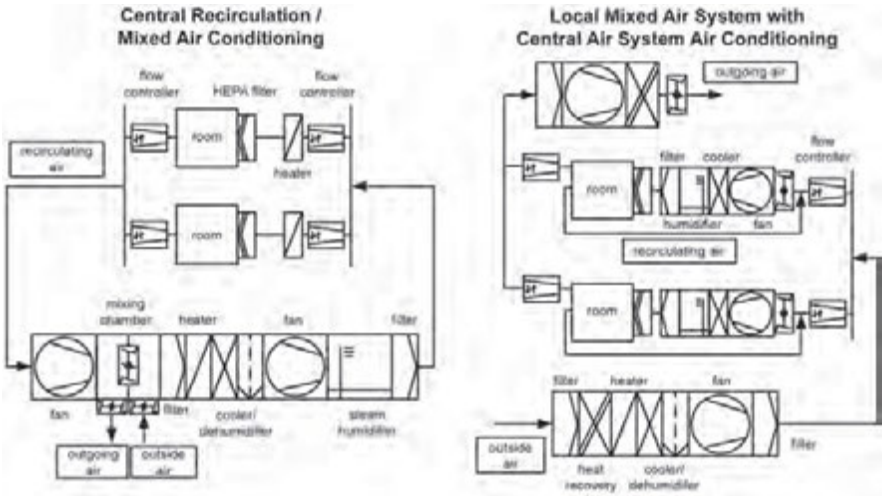

Figure 1. Most frequently used systems.

The maximum number of viables is also defined in the EU GMP Guideline. Annex 1 of this guideline divides clean rooms into four classes: A, B, C and D, where class A indicates the purest level and class D allows the highest level of maximum allowable particle and viable concentration. According to the international standard ISO 14644-1, clean rooms are classified from ISO 1 to ISO 9.

Airborne particles and viables can be reduced by increasing the air exchange rate. This number indicates how many times per hour the total air volume of a room is conveyed through the air handling unit with filter. Commonly a number of between 30 and 60 air changes are applied per hour for a class B room (ISO 7, in operation), and approx. 20 for a class C room (ISO 8, in operation). Class A areas (ISO 5) frequently require a Unidirectional Air Flow (UDAF) – mistakenly characterized as Laminar Flow (LF) – with a typical air velocity of 0.45 m/s ± 20%.[4,5]

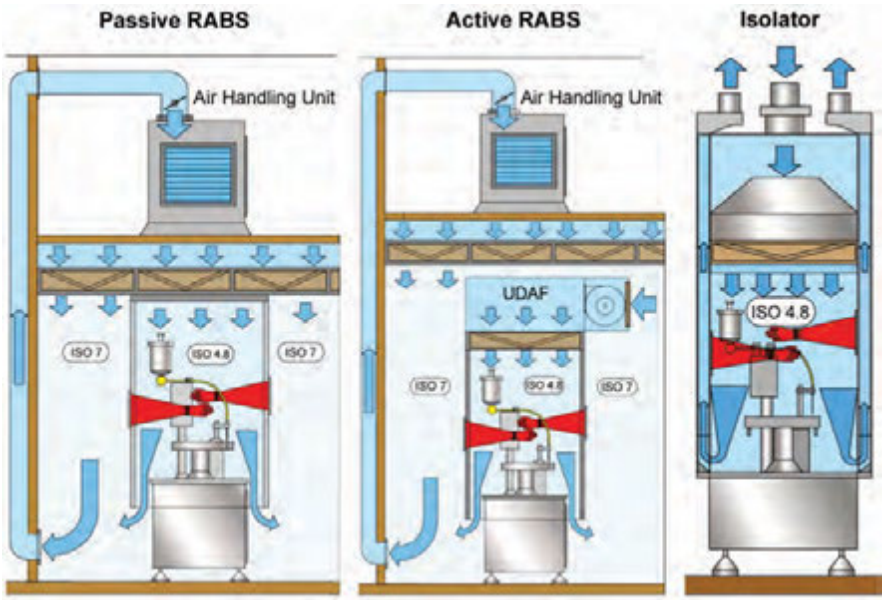

Figure 2. Barrier systems.

Barrier Technologies

People are the main source of particle contamination in aseptic filling operations. To minimize the risk of microbiological contamination, the access of operators should be restricted. Based on this requirement different concepts have been developed in pharmaceutical filling technology to address the demanded purity specifications. Barrier systems like RABS and isolators are suited to avoid undesirable contamination of products.

Restricted Access Barrier Systems (RABS)

RABS is a production area that has a rigid machine enclosure, safety-locked doors and ports with gloves. It provides a physical barrier between the production area and the operator environment. RABS must always be installed in a class B clean room (ISO 7, in operation). Different types of RABS, such as closed RABS with air recirculation, and open RABS with air overflow into the clean room are typically applied to fill/finish operations. Depending on the kind of aeration, a distinction is made between passive and active RABS. The passive RABS has no aeration equipment; however, UDAF is supplied by the filter fan unit integrated in the ceiling of the clean room. An active RABS has its own aeration and filtration equipment as seen in Figure 2. The air is directly taken from the clean room. The UDAF fans are independent from the clean room aeration and are directly placed onto the RABS processing area.[6]

Isolators

An isolator is a hermetically sealed system with a complete separation of operator and process area. Doors cannot be opened during production, which makes it possible to operate isolators in a class C clean room environment (ISO 8, in operation). The UDAF inside the isolator is similar to the one inside a RABS. An isolator is typically equipped with a system for bio-decontamination and an air handling unit that ensures temperature control by heating or cooling, as well as permanent overpressure control of the process area compared to the operator environment in order to avoid ingress of

contaminated air. The air can be dehumidified by a dryer for the preparation of bio-decontamination, and if necessary, also during production, for example, to avoid condensation on fill hoses during cold product fill operation. After sterilants, such as evaporated hydrogen peroxide (VPHP), are ducted into the isolator during bio-decontamination, the isolator is either aerated with fresh outside air or via recirculation with a catalyst. There are several possibilities to implement the isolator's aeration equipment into the technical building services, of which three are investigated and discussed below.[7]

Air Conditions During Air Handling

In order to calculate the overall energy consumption, changes in air conditions must be considered for each consumer. To receive defined air conditions, e.g., 20°C (68°F) at an absolute humidity of 5 to 9 g/kg, the air has to be heated, cooled, dehumidified or humidified depending on the outside air conditions. Mixing chamber, heat recovery unit and temperature increase caused by the electric motors of fans or light sources also must be taken into account. The psychrometric chart clearly illustrates changes in air conditions through heating, cooling, dehumidification and humidification as well as mixing of air volumes with different conditions. Figure 3 shows an example of a central recirculation/mixed air conditioning system for warm and humid air during summer time (OA_{SU}). First of all, the outside air volume flow (e.g., 20%) is mixed with the room air volume flow RA_{SU},(Point 4) resulting in a new air condition MA_{SU} which is located on the connecting line of the two initial points. The position of this mixing point MA_{SU} can be related to the reciprocal ratio of the air volume flow rates. The air that is still too warm and too humid is cooled down by the cooler until it undercuts the dew point and the water begins to condense. At an absolute humidity of 9 g/kg the air is heated up until it reaches the required temperature (SA_{SU}) (Point 6). During winter time, the initial position is exactly opposite. The cold and dry outside air (OA_{WI}) is mixed with the room air flow (RA_{WI}) (Point 1). The mixed air MA_{WI} is then heated (Point 2) and humidified with steam up to an absolute humidity of 5 g/kg (SA_{WI}) (Point 3). Humidification with steam of 100°C is almost an isothermal process; the increase in temperature is marginal.

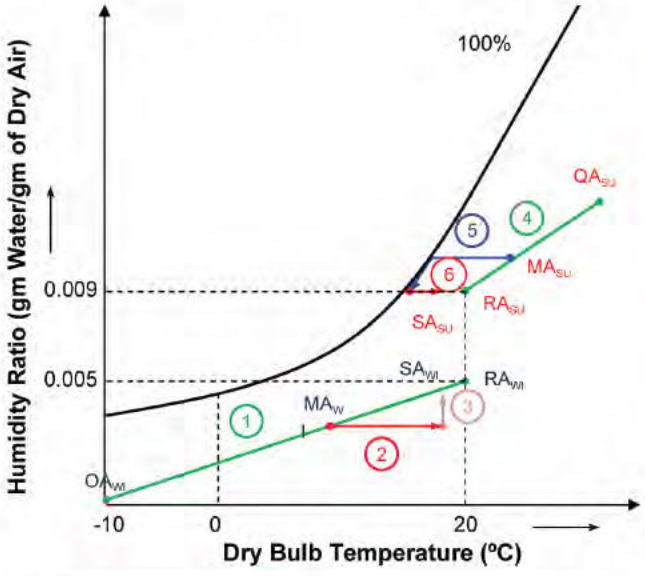

Figure 3. Pyschrometric chart.

Installation Concepts

The following paragraphs will provide an analysis of the differences in energy consumption between passive and active RABS and isolators.

Passive and active RABS as seen in Figure 4 are directly or indirectly supplied with air by the technical building services. A passive RABS is sealed to the ceiling of a class B clean room. It is considered as a class A clean room (ISO 5) with

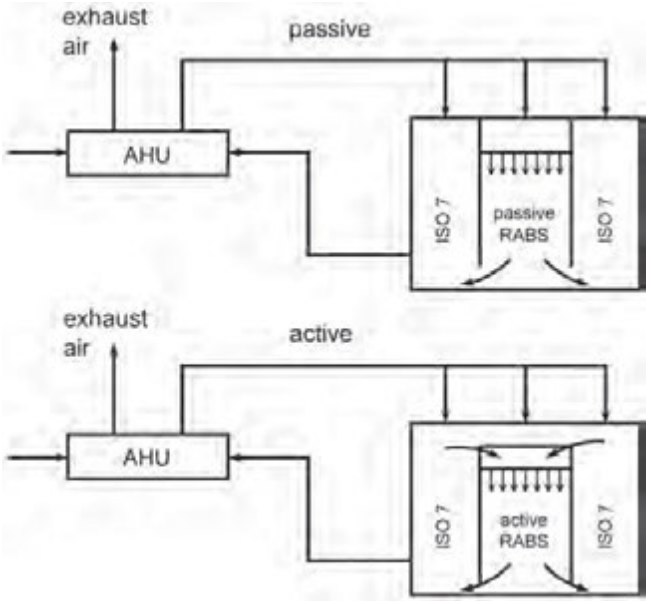

Figure 4. RABS systems.

UDAF. The footprint of the passive RABS can thus be deducted from the area of the surrounding class B clean room (ISO 7, in operation). The active RABS, in turn, is equipped with self-contained air handling equipment. It is not attached to a certain place; therefore, it is not included in the calculation of the clean room area size and the required air flow rates.

Isolators as seen in Figure 5 are equipped with a proprietary process air handling unit (process AHU) which dissipates internal heat loads and corresponds to the special requirements of bio-decontamination. A defined amount of fresh air is supplied to the isolator as a result of temperature control, overflow of air to the clean room, for instance, through mouse holes, and pressure control. In the following examples, the air exchange is only realized by the process air handling unit.

In example A, the process air handling unit is supplied by an additional outside air handling unit. The exhaust air is completely discharged to the outside. In example B, the process air handling unit only discharges the amount of air which is necessary to obtain the pressure level inside the isolator. This is done by an exhaust fan. The majority of the air volume is recirculated through a bypass, mixed with fresh air coming from the outside air handling unit, and supplied to the isolator again. While the isolator is being aerated after bio-decontamination, the air polluted by sterilants such as evaporated hydrogen peroxide (VPHP), is completely discharged to the outside, with or without passing a catalyst. Example C shows an option to use air directly from the surrounding clean room. Air is taken directly from the clean room or its exhaust piping system and is ducted to a process air handling unit. In this case, an outside air handling unit is not necessary. The exhaust air of the isolator is discharged to the outside. Depending on size, air change rate and fresh air ratio of the clean room, this portion of the exhaust air volume would be discharged to the outside in any case. A disadvantage of this very efficient solution is that pressure and air flow rates of the isolator cannot be controlled independently from the clean room, as it may influence the pressure control of the clean room. Instead of discharging it from the isolator, the exhaust air could be circulated to the clean room again. In this case, a catalyst would be necessary for the aeration process following bio-decontamination to reduce the VPHP concentration to a point below the occupational exposure limit. Figure 4 shows the RABS and Figure 5 the isolator systems.

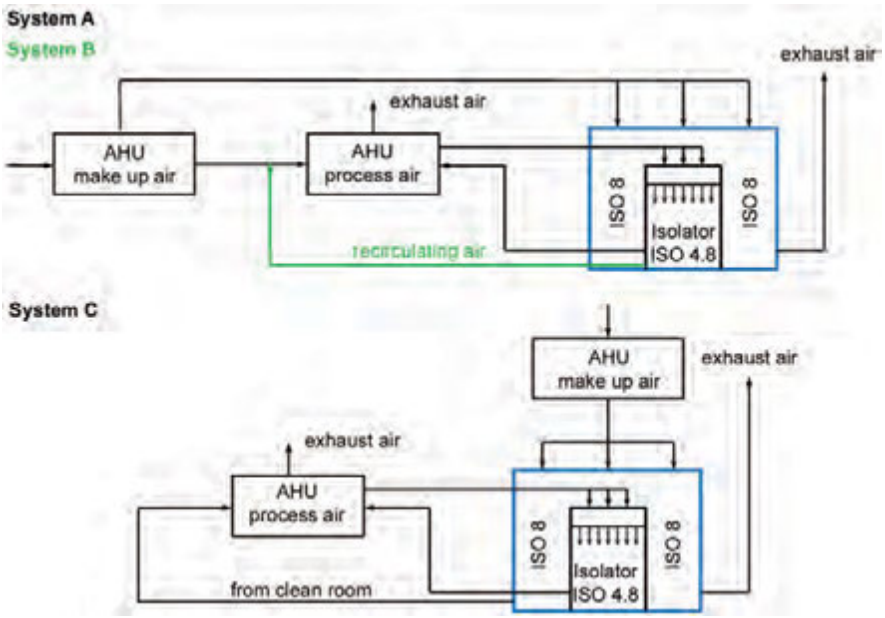

Figure 5. Isolator systems.

Table A shows the components of the air handling units and the typically used media/energy sources and exemplary values.

Important Assumptions

A number of boundary conditions (partly shown in Table B) are required for the calculation of energy consumption. This specific data can have a large impact on the results. A comparison of the energy consumption of different barrier systems is only possible for a specific situation and should be recalculated on the basis of the different component characteristics. The following calculation is based on the parameters in Table B.

Results

The following comparisons were evaluated:

a. Comparison of technical building services – central recirculation/mixed air conditioning and local mixed air system with central outside air conditioning
b. Comparison of passive and active RABS and isolator by energy sources
c. Energy users of different isolator systems

Comparison of Technical Building Services

Figure 6 shows the total energy consumption of all energy users between central recirculation/mixed air conditioning (central recirculation) and a local mixed air system with central outside air conditioning (decentral recirculation) of passive RABS and isolator (configuration A).The total annual energy consumption of each system is split into the following components:

- RABS configuration
  - Clean room
  - Outside air conditioning of clean room and RABS
  - RABS enclosure
- Isolator configuration
  - Clean room
  - AHU outside air, clean room
  - Isolator
  - AHU process air, isolator
  - AHU outside air, isolator

The RABS configuration shows the same amount of proportional energy consumption for both the clean room and the passive RABS. It consists of the electrical power of the fans and is independent from the air handling unit. Compared to the central recirculation system, the energy savings of the decentral recirculation system is 33% or 409 MWh. The most significant difference is the power requirement of the fans, which accounts for 62% or 217 MWh. In the central recirculation air handling system, the air flow has to pass all components and long ducting distances, causing pressure drops which, in turn, must be compensated by the fans. In the decentral recirculation system, the air flow only needs to pass a cooler, a filter and a short ducting, so the required fan power is much lower. The second largest saving of 126 MWh is achieved by the chilled water supply for the coolers. The outside air has to be cooled down for dehumidification. In the central recirculation system, the overall air flow is cooled down and heated up again, while the decentral recirculation system only requires the fresh air

	Process	Medium	Parameters
AHU Outdoor Air	Heating	Hot Water	50°C (122°F) / 70°C (158°F)
	Cooling	Chilled Water	6°C (43°F) / 12°C (54° F)
	Humidification	Steam	120°C (248°F)
	Dehumidification	Chilled Water	6°C (43°F) / 12°C (54°F)
	Air Conveyance	Electricity, Fan	400 V (460 V)
AHU Process Air	Cooling	Chilled Water	6°C (43°F) / 12°C (54°F)
	Dehumidification	Desiccant Rotor	
	Heating/ regeneration of desiccant rotor	Steam	3 bar absolute
Passive RABS	-	-	-
Active RABS	Air Conveyance	Electricity, Fan	400 V (460V)
Isolator	Air Conveyance	Electricity, Fan	400 V (460V)

Table A. Media requirements for air conditioning.

	RABS	Isolator
Room size	Class A (ISO 5) = 19m^2 (205 sq ft) Class B (ISO 7, in operation) = 221 m^2	Class A (ISO 5) = 11 m^2 (118 sq ft) Class B (ISO 7, in operation) = 0 m^2 (0 sq ft) Class C (ISO 8, in operation) = 201 m^2 (2164 sq ft)
Change of air ventilation	Class A (ISO 5) 0.45 m/s Class B (ISO 7, in operation) 40 1/h Class C/D (ISO 8, in operation) 20 1/h	
Fresh air rate	20%	
Clean room temperature regulated	5 to 9 g/kg absolute humidity	
Outside air temperatures to VDI 4710 Part 3 2011-03 (8)	Location: central Europe, Germany, Mannheim	
Heat recovery rate	0.6	
Thermal load clean room	60 W/m^2 (5.6 W/sq ft)	
Thermal load RABS/Isolator	850 W/m^2 (79 W/sq ft)	

Table B. Assumptions for calculation.

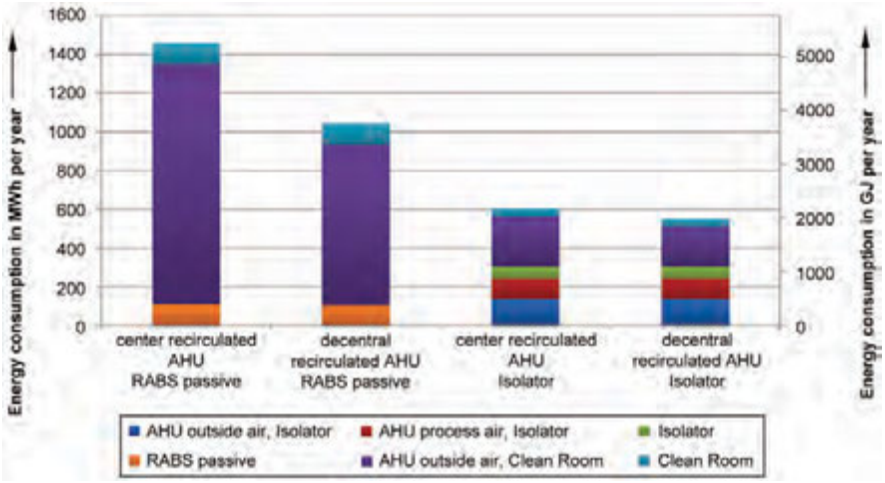

Figure 6. Building services.

volume (e.g., 20%) to be chilled for dehumidification. The remaining energy savings can be related to the hot water system (65 MWh). There is no difference in energy consumption when the air is humidified by steam. The result largely depends on the efficiency of the heat recovery system of the local mixed air system with central outside air conditioning.

Similar to the RABS configuration, an isolator configuration with a decentral recirculation system consumes less energy. However, the smaller clean room volume and lower air flow rates only result in a difference of 52 MWh between a central and decentral recirculation system, which is significantly smaller than for the RABS configuration. The outside air handling of the isolator is hardly affected because the air is only conditioned once before it is put out to the process air handling unit of the isolator. Central recirculation/mixed air conditioning being very common in the pharmaceutical industry, all following calculations are based thereon.

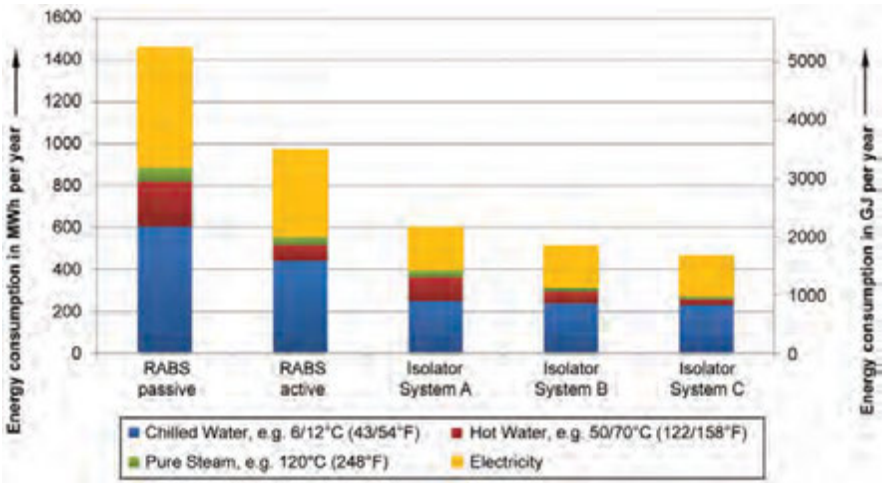

Figure 7. Energy consumption differentiated by energy sources.

Comparison of Passive and Active RABS and Isolator by Energy Sources

Figure 7 shows the overall annual energy consumption, divided into the energy sources cold water, hot water, steam and electricity.

The energy consumption of an active RABS is 35% or 517 MWh less than for a passive RABS. Depending on the isolator system A, B or C, energy savings of up to 69% are possible compared to a passive RABS. While a passive RABS is completely supplied by fresh pre-conditioned air, an active RABS gets the pre-conditioned air directly from the clean room. At the same outdoor air percentage (e.g., 20%), the passive RABS shows a higher outside air flow rate. This difference directly relates to the reduced amount of steam required for humidification and electrical power required for outside air handling. The power required for the fans of clean room and active and passive RABS remains almost the same.

The demand for cold and hot water depends on different parameters. Chilled water is used for dehumidification and chilling of the outside air (especially in summer time) in order to dissipate the heat load in the room. The heat load defines the supply air temperature depending on the air flow rate. The internal heat loads of an active and passive RABS are almost identical. When clean room and RABS are the same size, they use the same heat sources like fans, lights, fill/finish equipment drives and also human operators, which all have an impact on the room temperature.

Due to the high air change rate (high air flow rate) of a passive RABS, the temperature difference between room and supply air is relatively small (e.g., 1.5 Kelvin). The temperature between room and supply air must be higher for an active RABS (e.g., 4 Kelvin) owing to a lower air flow rate at the same heat load. Smaller air flow rates at colder supply air temperatures of an active RABS lead to a saving up to 64% compared to a passive RABS. The savings in chilled water only amount to 27%, as the heat load is the same for both RABS and has to be dissipated by the chilled water system. This saving results from the smaller outside air volume to be handled.

The main differences between RABS and isolator system in regard to energy consumption consist in the smaller clean room space required and the lower clas-

sification of the surrounding clean room. Additionally, the area of the class A (ISO 4.8) clean room is smaller due to the more compact design of the isolator. The UDAF of the RABS is larger than its footprint. The power consumption of the three isolator systems shown in Figure 7 is itemized for the different system components in Figure 8.

Energy Users of Different Isolator Systems

The outside air handling unit of the isolator systems A, B and C are shown separately. The process air handling unit, the isolator, the air handling unit of the clean room and the clean room itself are identical for all three systems, which is why they are only shown once for all three systems in Figure 8.

The only ventilation technology consumers of the isolator and the clean room are electrically powered fans. The air handling unit of the clean room has a high demand for chilled water due to the heat loads. Heat loads and low air change rates originating in the relatively low clean room classification require a supply air temperature of 16°C (61°F) for the clean room environment of the isolator system. In order to obtain this supply air temperature, the mixed air must even be cooled at outside air temperatures of 0°C (32°F). For example, air from the clean room (20°C/68°F, 80% volume percent) is mixed to 16°C (61°F) in the mixing chamber with outside air (0°C/32°F, 20% volume percent). Because the air is heated to 17°C (63°F) by the fan, cooling is necessary. While the supply air for the clean room mainly consists of recirculated air, a lot of cold water is required for cooling purposes. The energy consumption of outdoor air conditioning depends on the location. Weather data[8] of a location in Central Europe (Mannheim, Germany) serves as basis for this calculation.

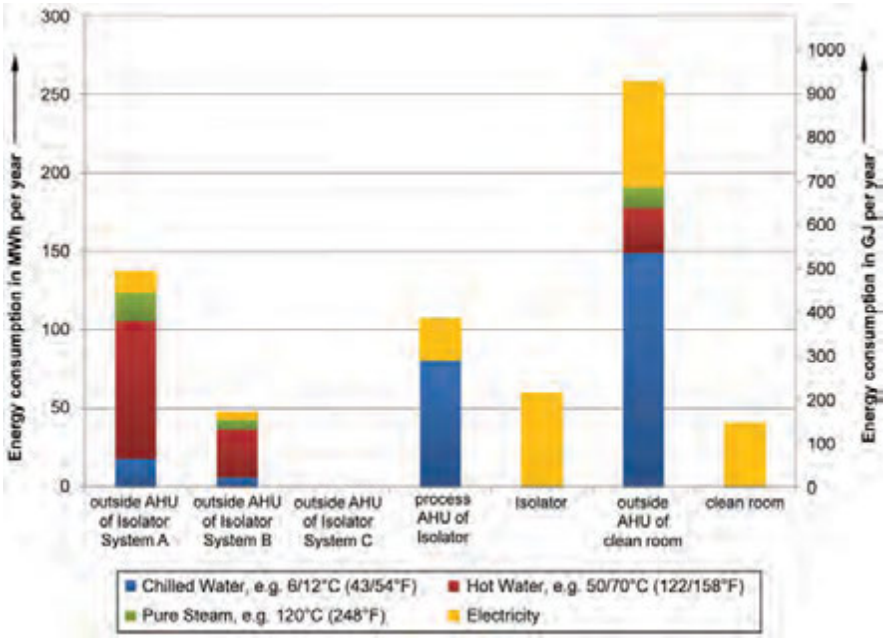

Figure 8. Energy consumption of three isolator systems.

The process air handling unit of the isolator controls the temperature in the isolator. Because of the isolator's heat loads, it needs a lot of chilled water. Heating of the air in the process air handling unit is not considered in this example. However, hot air provided by an electric heater or steam flow heat exchanger is required to regenerate the desiccant rotor. In this case, the energy consumption is very low, because the duration of the drying cycles at two bio-decontamination cycles per week equals a maximum of only one hour per week.

The outdoor air handling unit of system A has the highest energy consumption (137 MWh). The consumption of system B, which is a recirculation system, amounts to 48 MWh. It saves 65% of energy. The overall energy saving of the complete system including clean room results in 15%.

System C does not require an outside air handling unit. Compared to system A, it could achieve an energy saving of 23%. The isolator is supplied with air directly from the clean room or with exhaust air. The advantage is that no additional outside air must be conditioned for the clean room, as its exhaust air would have been discharged in any case, owing to to the fresh air portion requirement of the supply air. In case the air handling unit of the clean room has to supply additional air volume for aeration after bio-decontamination, the annual additional power demand at two cycles per week would be 6 MWh.

A further possibility consists in taking air from the surrounding clean room and giving it back again. This also would not require any outside air handling. After bio-decontamination, VPHP must be decomposed by a catalyst during aeration. Similar to system C, the influence of the air exchange between isolator and clean room on the pressure control of the clean room must be taken into account.

Summary

This discussion has compared the most common types of technical building services, central recirculation/mixed air conditioning and local mixed air systems with central outside air conditioning in regard to energy consumption. It also presented the energy consumption of passive and active RABS and isolators with three different air handling unit systems.

The direct comparison of the technical building services shows that the local mixed air system with central outside air conditioning is the best solution regarding efficiency for both RABS and isolator. Higher air volumes make the difference for RABS considerably high (33%). One energy-related advantage is that the recirculating air does not need to pass all system components. Moreover, only the

very small fresh air rate needs to be cooled down for drying.

The comparison of passive and active RABS has shown that the active RABS requires significantly less energy. It uses conditioned air from the clean room. Through this double usage, the system requires a smaller fresh air flow rate, which results in energy savings.

The energy difference between RABS and isolator systems arises from the smaller clean room space and the lower requirements of the lower clean room classification. The isolator system can be operated in a class C clean room (ISO 8, in operation) while a RABS needs a surrounding clean room of class B (ISO 7, in operation). Higher air change rates and additional areas for air locks, dressing rooms etc., are also necessary for RABS. Depending on the isolator system, energy savings of 69% are possible compared to the passive RABS.

The isolator system can be integrated into the technical building services in various ways. From an energetic point of view, it is desirable that as little as possible outside air must be prepared for the isolator. The use of the air recirculation system in the process air handling unit significantly reduces the outside air flow rate. The air for the isolator system also can be taken from the exhaust air of the clean room. In this case, no outside air needs to be conditioned, which would be the most energy-efficient solution.

This comparative calculation depends on many parameters and has been carried out by way of example. Each system, location, room size, air exchange rate etc., can highly affect the results; therefore, every system requires an individual calculation. However, the main conclusions of this study should be applicable to a large number of situations.

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The Application of Cogeneration for Pharmaceutical Facilities

by Joseph F. Masiello, PE CEM LEED AP

This article presents how the pharmaceutical industry has various unique characteristics, along with the various issues of concern for those in the industry contemplating the use of cogeneration.

Cogeneration, defined as the sequential generation of heat and power from a single fuel source, has become a very viable utility/energy option for pharmaceutical facilities, and as such, it is worthy of serious consideration. This is particularly true given the energy consumption characteristics of the industry, in which production facilities operate with multiple shifts, often six or seven days per week. These facilities customarily require the generation/provision of heating and cooling year round for process and HVAC loads; and the sophisticated equipment and critical operations require clean (high power factor) and reliable power.

With these characteristics, as well as the improved cycle efficiencies of today's equipment and the use of natural gas as the primary fuel, many in the industry have found the cogeneration systems, wherein electric power is generated and the heat created in that process is recovered and put to use, to be economically and environmentally beneficial.

There are numerous issues related to the implementation of cogeneration projects and a considerable amount of study and analysis is required from the determination of feasibility through the detailed design and construction of the projects. Economic, regulatory, legal and technical issues must all be thoroughly evaluated on a case-by-case basis.

Although this narrative is general in nature, an emphasis is placed on "small power" (25 MW and under) cogeneration/combined heat and power (CHP) systems and their application to pharmaceutical facilities. The pharmaceutical industry has various unique characteristics that will be addressed throughout this article along with the various issues of concern for those in the industry contemplating the use of cogeneration.

Legislative and Environmental Aspects of the Power Industry

Regulatory/Legal Issues

Since the 19th century, power generation has changed and so has the legislation governing these matters. It is helpful to look at the evolution of this legislation and its current status, as the climate today seems to be growing progressively more hospitable for cogeneration.

In the late 19th and early 20th century, the majority of the U.S. electric power generating stations operated on a small scale basis and were owned by private individuals or publicly owned/non-regulated utility companies. During the great economic expansion of the 1940s through 1970s, numerous large scale utility plants were built. These utilities came under governmental control, which guaranteed a "reasonable profit" to the utility companies. Over time, electric rates increased and a consensus was reached that electric power costs were generally high (this is highly variant depending on the fuel used to generate power, local utility costs, and governmental regulations that contributed to higher costs, etc.)

At present, (since the beginning of the 20th century and then gaining momentum in the 1940s), the majority of the power generated in the United States is provided by publicly owned (with government ownership in various cases) electric utility companies. During the 1970s (under the Carter Administration), legislation was passed that encouraged the expansion of independent cogenerators.

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Independent Power Producers (IPPs) are power stations that generate power and sell the power to the public utility company at the point of interconnection. The government entity, Federal Energy Regulatory Commission (FERC), which would oversee any concerns, was created when the Public Utilities Regulating Policy Act (PURPA) legislation was passed. In time, it was discovered that cogenerators could actually benefit utilities in certain circumstances, such as when the utilities are operating at near full capacity and are experiencing increased loads on the grid. The cogenerator could remove the burden of providing additional generating capacity that otherwise the utility company would have to provide. Many guidelines were included that encompassed the quality of power the cogenerator was to provide, the means of arriving at the rates the cogenerator could charge (commonly referred to as "avoided cost"), necessary protection to be provided to the utility grid, etc. Government regulations need to be understood and verified by the owner/operators on both the local and national levels prior to making significant commitments.

Although legal/regulatory narrative cited herein is oriented to the U.S., similar issues exist in all industrialized nations with a robust power grid and active governmental oversight.

Environmental Issues

Similar to the progression of legislation regarding power generation, environmental concerns about air quality and the potential effect of power generation on it have led to changes in awareness and legislation. These concerns and resulting legislation may have an impact on a facility's decision to move toward cogeneration.

During the mid- 20th century, many localities in the U.S. were enacting air pollution control legislation. In 1955, the first Federal Legislation "Air Pollution Control Act of 1955" was passed. This law contained language stating that air pollution was a national problem and called for continued research in the area.

Eight years later, Congress passed the nations Clean Air Act of 1963. This act dealt with reducing air pollution by setting emissions standards for stationary sources such as power plants and steel mills. It did not take into account mobile sources of air pollution, which had become the largest source of many dangerous pollutants.

The issue was addressed again in 1970. Although important legislative precedents had been set, the existing laws were deemed inadequate. While technically an amendment, the Clean Air Act of 1970 was a major revision and set much more demanding standards. It established new primary and secondary standards for ambient air quality, set new limits on emissions from stationary and mobile sources to be enforced by both State and Federal governments, and increased funds for air pollution research.

In 1990, after a period of regulatory restraint, the federal government believed that the Clean Air Act should again be revised due to growing environmental concerns. The Clean Air Act Amendments of 1990 addressed five main areas: air-quality standards, motor vehicle emissions and alternative fuels, toxic air pollutants, acid rain, and stratospheric ozone depletion. In many ways, this law's objective was to strengthen and improve existing regulations.

The 1990 CAAAs require that states establish certain emission criteria in terms of the localities being "attainment" or "non-attainment" areas. Emissions control devices, in many cases, might be required depending upon these factors as well as the amount of Nitric Oxide Compounds (NOX), Sulfur Dioxide (SO_2), un-burnt hydrocarbons (UHC), and Carbon Monoxide (CO), etc. emitted during combustion processes.

Emissions generating equipment above 10MM btu/hr generally requires permitting. In many states, it is required to have emissions reducing equipment if more than 25 tons/yr of hazardous air pollutants are discharged from the equipment (referred to as a "major source"). Air Permit Reports need to be issued to the public authorities to qualify these issues prior to receiving permission to execute projects of this nature.

Energy Cost and Load Profiles of Typical Facilities

Pharmaceutical manufacturing and research facilities utilize

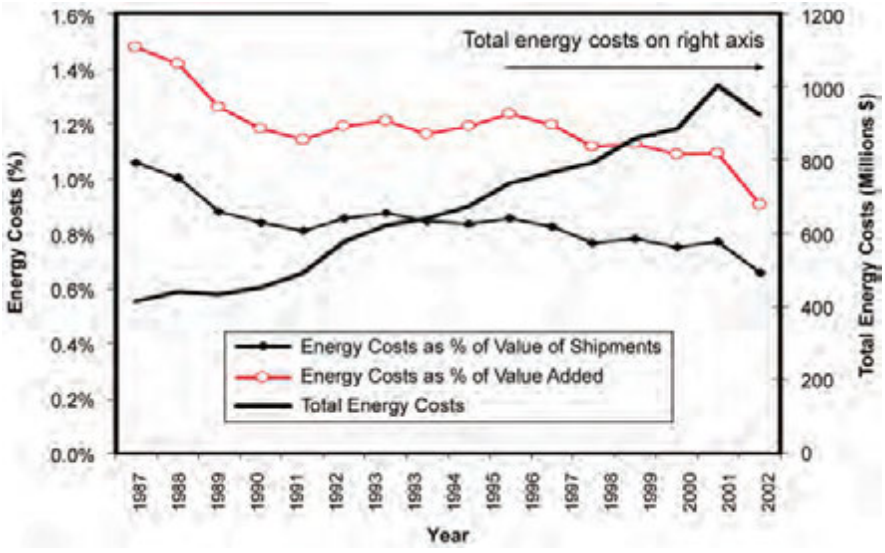


Figure 1. Trends for energy costs in the pharmaceutical industry as a whole over a 15-year period (1987 – 2002) (Sources: US Census (1990, 1993, 1995, 1996, 1998, 2003, and 2005a)).

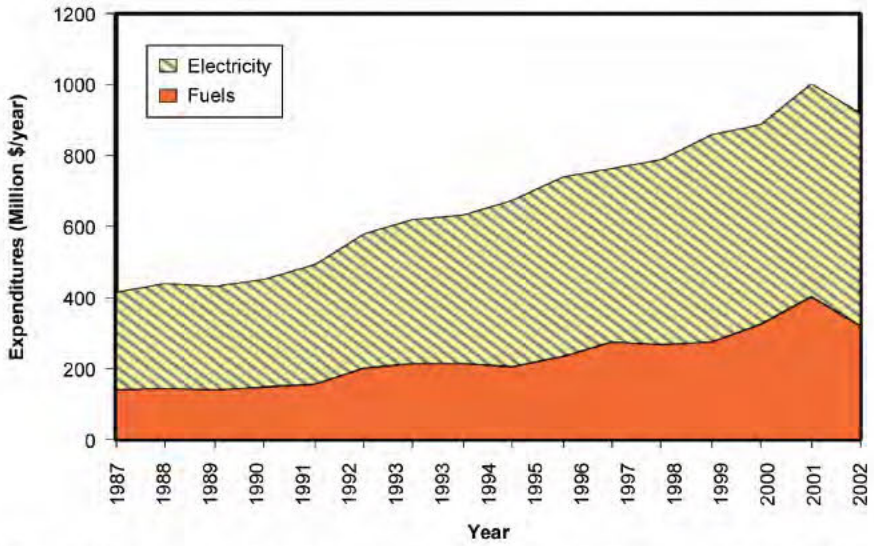


Figure 2. Fuel usage and electric power consumption (Sources: US Census (1990, 1993, 1995, 1996, 1998, 2003, and 2005a)).

energy intensive processes that often operate on a 24/7/360 day basis per year. In particular, multiple shift operations and working through weekends is commonplace in these manufacturing facilities. These operations customarily require the simultaneous generation of heating, cooling and electrical power year round – for both process and HVAC loads. Additionally, the sophisticated equipment in these facilities requires clean (high power factor) and reliable power. The combination of these factors often makes cogeneration/combined heat and power worthy of consideration.

Before addressing in more detail the energy and load aspects of these facilities, the trends in energy use and costs from an industry historical perspective will be reviewed. Figure 1 depicts trends for energy costs in the pharmaceutical industry as a whole over a 15-year period (1987 to 2002). The data provides a few interesting observations: the cost of energy is decreasing as a percentage of the value of the products overall, but is increasing in real [actual] cost. This would be a parameter to be considered by the owner. If the cost of energy relative to overall income is small (varying between .8% and 1.5%), should it be rigorously considered? Or is energy consumption and the commensurate savings (both from a sustainability and economic view) considered to be a critical issue for the company?

Figure 2 divides the energy costs into fuel usage and electric power consumption. The trending data here shows the actual [real] costs of energy (fuel and electricity) are rising. But more interestingly, the spread in the costs between fuel and electricity is *increasing* (Today, the spread is considerably larger considering the lower cost of natural gas). This trend favors the economics of cogeneration.

Figure 3 depicts the historical relationship between electric power purchased by pharmaceutical manufacturers and power generated by those manufacturers, which is particularly relevant to the thesis of this article. In 1987, about 95.2% of power used by pharmaceutical manufacturers was purchased whereas 4.8% was generated by them. By 2002, the percentage of generation by the facility rose to 10.8% - a bit more than doubled. The opportunities to increase the 10.8% value are worth exploring, meaning that the overall economics may be very positive for the remaining 89.2% of facilities that purchase power from their respective local utility company.

Cogeneration Systems and Equipment

The technical aspects of cogeneration systems involve numerous elements ranging from equipment to general construction materials. In terms of power generating equipment (commonly referred to as "prime movers"), the following are the most commonly used:

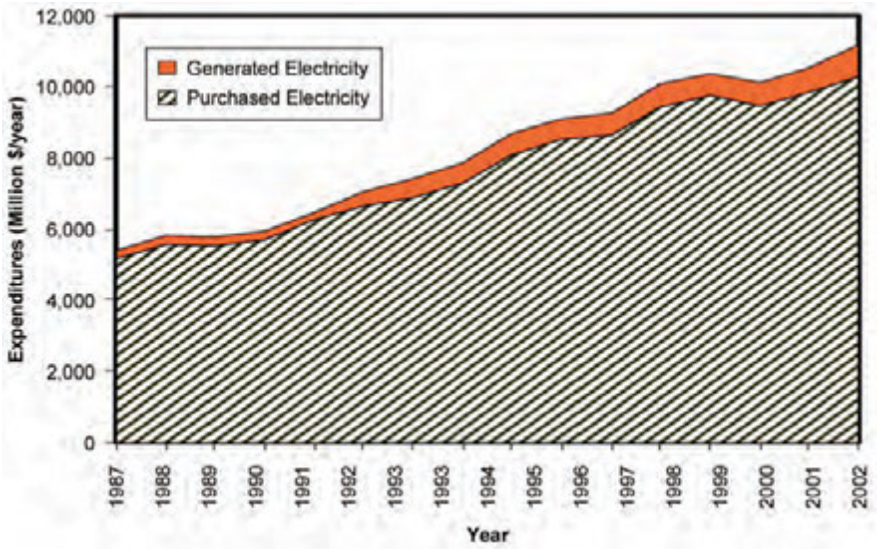


Figure 3. Historical relationship between electric power purchased by pharmaceutical manufacturers and power generated by those manufacturers.

- Combustion (Gas) Turbine Generators
- Reciprocating Engines
- Steam Turbine Generators

These power operating devices have different operational characteristics and are used differently in the variety of cogeneration applications summarized below.

Combustion (Gas) Turbine Generators (CTGs)

Combustion turbine generators as seen in Figure 4 may be procured as natural gas fired, distillate oil fired, or dual fuel. Combustion turbine generator sets typically deliver mechanical efficiencies in the 30% (small units – 3.0 MW and under) to 38% (larger units – 40 MW and above) range. These units are configured with the following primary components.

- Compressor – the compressor takes in ambient air and compresses the air to a pressure ranging from 175 psig to 750 psig. The compressed air is utilized for combustion and/or by-passed for cooling the inner turbine components.

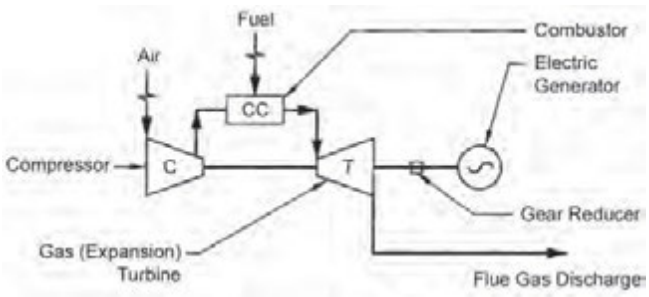


Figure 4. Combustion turbine generator configuration.

- Combustor – the combustor mixes the combustion air and the fuel and then ignites them causing a rapid pressure rise in the combustion chamber.
- Gas Turbine (Expansion) – the hot gases are under high pressure are then expanded out of the turbine section of the unit and discharged to atmosphere.
- Gear Reducer – a gear reducer is typically provided between the turbine rotor and the operator in order to adjust the rotational speed differential.
- Electric Generator – the generator is typically of the synchronous type and produces electric power at the voltage, frequency and phase angle.

The characteristics most unique to the CTG set is the high volume of high grade heat available from the turbine (typically ranging between 750° to 950°F). The flue gases discharging from the CTG are capable of generating high temperature water or high pressure steam. In addition, the oxygen rich gas discharge (typically 12 to 15% O_2) can be additionally "fired" and boost the exhaust gases to much higher temperatures. This heat content is capable of generating considerable levels of high heat for thermal distribution, additional power generation, or mechanical work. These sets are customarily supplied with weather/sound enclosures and have ancillary components such as lube oil coolers, intake air filter banks, and flue gas stacks.

Reciprocating Engines

Reciprocating engines as seen in Figure 5 come in a variety of sizes and power capacities generally in the range of 25 KW to 10 MW. They are typically supplied as diesel oil fired, natural gas fired, or "bi-fuel" meaning same engines mix and simultaneously burn fuel that is utilized in generating mechanical work, electrical power, and heat. The speed of reciprocity engines varies between 400 rpm (durable-continuous duty operation) and 1800 rpm (non-continuous duty/peaking power).

The primary components associated with these engine/generator sets are as follows:

- Reciprocating Engine – engines are generally gaseous or liquid fuel fired and the combustion process generates heat that is transferred from the engine jacket to a heat exchanger/radiator.
- Gear Box – the gear reducer/increaser compensates for the rotational speed of the engine necessary for the electric generator.

- Electric Generator – the generator generates electric power at the proper voltage, KW and frequency. The generator is generally of the synchronous type.
- Heat Recovery Steam Generator/ Silencer – the exhaust (heat recovery) silencer attenuates the flue gases that discharge from the engine. The silencer often has a heat exchanger that is capable of providing high grade heat in small quantities.
- Radiator (Heat Sink) – a radiator/ heat exchanger is utilized to remove heat generated in the system jacket. This (low grade) heat may be recovered by a heat exchanger and used for energy recovery or rejected to atmosphere. The radiator and engine jacket are typically connected with piping and a circulating pump.

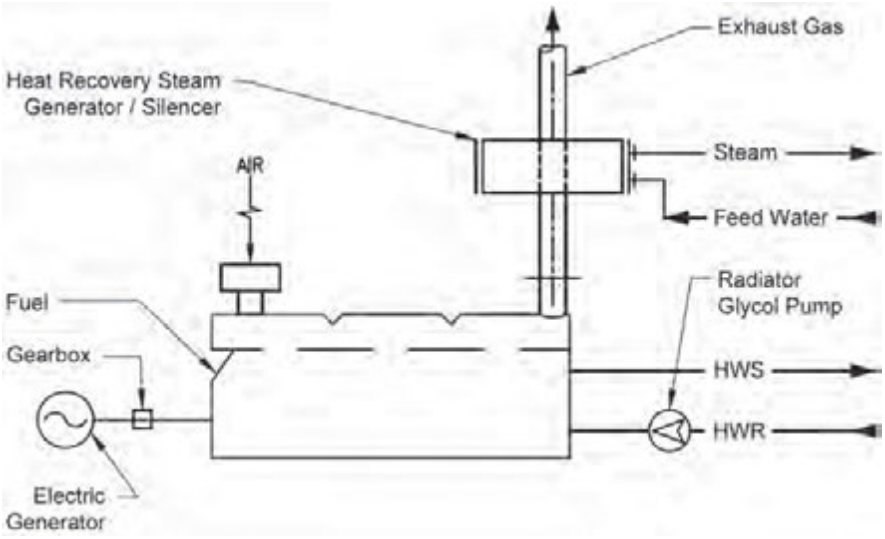


Figure 5. Reciprocating engine with jacket and exhaust gas heat recovery.

Reciprocating engines typically operate at mechanical efficiencies of 30% to 41%. The characteristic most fundamental to the reciprocating engine scheme is the provision of "low grade heat" meaning that the temperature of the jacket cooling water is only about 180° (but it is approximately 30% of the available heat for recovery). There is higher temperature heat from the flue gases, but it is only about 12% of the system rejected heat. Depending upon the facility process/ HVAC loads, the temperature of the jacket water may or may not be a constraint.

Steam Turbine Generators

Steam Turbine Generators (STGs) may be provided with several different configurations. The turbine generator sets utilize gear reducers and generators similar to the configuration of gas turbines, but they often need ancillary heat exchangers for seal cooling and cooling towers for condensing turbines.

The typical configurations are as follows:

- Condensing Turbine – the condensing turbine has a discharge pressure that is held below atmospheric, typically 2.5 to 3.0 Hg. This generally produces a large drop across the turbine converting the energy to mechanical shaft work in the most effective manner.
- Backpressure (non-condensing) Turbine – this backpressure turbine has a discharge pressure that is held above atmospheric pressure to often meet a process or heating requirement.
- Condensing/Extraction Turbine – the condensing/extraction turbine has a condensing port (at 2.5 to 3.0 in Hg.) and an extraction port that may deliver low or high pressure steam depending on the project needs.

The steam loads at a facility usually dictate which turbine is the most effective for use. Steam distribution that is only higher pressure tends to favor backpressure turbines whereas high and low pressure distribution favors extraction stage/backpressure types. Systems without heating or process needs tend to favor condensing turbines.

Heat Recover Boiler

The Heat Recover Boiler (HRB) or more commonly called Heat Recovery Steam Generator (HRSG) utilizes the exhaust gases from a combustion turbine generator Set (or reciprocating engine) to generate steam or hot water. These HRSGs may be of a water wall or solid/refractory wall configuration. The boilers are generally of configuration with upper and

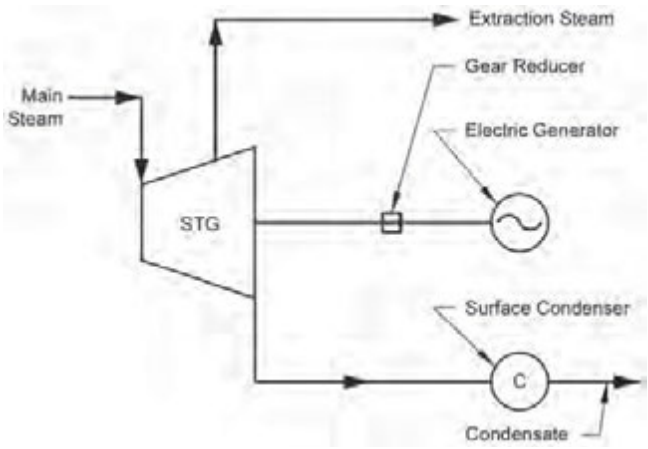


Figure 6. Condensing/extration steam turbine configuration.

lower steam drums. Superheaters are provided depending on the system requirements.

The following are the primary elements of an HRSG package:

- Inlet Bypass Valve and Relief Stack – this device directs the hot flue gases for the CTG set to the HRSG or discharges into the atmosphere.
- Duct Burner – this device fires fuel into the flue gases (that are oxygen rich) and boosts the temperature of the gases in order to generate more steam.
- Economizer – typically boilers above 150 psig operating pressure provide heat exchangers that reduce stack temperature by raising the water temperature to the HRSG/boiler.
- Fuel Train(s) – these devices have the necessary valves and safety controls to regulate the fuel flow to the burner.
- Flue/Exhaust Stack – discharges the flue gases from the boiler to the atmosphere.

HRSGs may generate high temperature water, saturated steam, or superheated steam, depending on the process requirements.

Balance of Plant Equipment

Balance of Plant (BOP) equipment is a term used to define the ancillary equipment that is part of the cogeneration system. The BOP equipment most relevant to these systems is as follows:

- Auxiliary Boiler(s) – generally, a "packaged" boiler that is capable of generating steam if the CTG/HRSG is off-line or to meet a steam load higher than the HRSG is capable of producing.
- Deaerator Tank – a storage vessel generally held slightly above atmospheric pressure. This water is fed into the HRSG/boiler. Prior to delivery to the boiler, the free oxygen in the water is removed to minimize boiler corrosion.
- Boiler Feed Water Pumps – these pumps transfer water from the deaerator to the HRSG/boiler.
- Condensate Receiver – condensate storage vessel that utilizes transfer pumps to fill the deaerator tank.
- Piping – for all services including steam, feed water, cooling water, compressed air, softened water, etc.
- Water Pretreatment System – the devices include water softeners, break tanks, deionization equipment, etc. These systems supply a more purified form of water that reduces corrosion and deposits in boiler tubes, or turbine blades, etc.
- Gas Compressors – the devices raise the pressure of the utility gas (pressures can vary from inwg to 200 psig or more) to the level required by the CTG (and possibly HRSG duct burner).
- Fuel Oil System – fuel oil tanks and pumps that provide fuel oil for the CTG and HRSG burners as needed.
- Cooling Towers/Radiators – these reject surplus of unused heat from the process.
- Compressed Air System – the air compressors, receiver tank, and ancillary devices needed to provide compressed air for the cogeneration system components.

These devices are all integrated together as part of a single system via the plant controls system. This equipment performs the system support functions that allow the heat and power to be generated and delivered to the respective users.

Special Engineering Considerations

The mechanical engineering design and analysis necessary to successfully construct and operate a cogeneration facility is considerable. The types of analyses cited below generally require computer software programs because of the extensive numerical computations required. These analyses techniques are:

- Heat and Mass Energy Balance – calculations of the air/fuel input, mass and energy levels of all fluid streams in the plant (fuel input, flue gases, steam flows, etc.)
- Thermal Pipe Stress Analysis – analysis of the static and dynamic conditions of the piping. Pipe stress levels and calculated to insure against over-stressing of any system components (piping, valves, etc.)
- Hydronic Flow Analysis – analysis of the flows and pressure drops throughout the various pumping systems.

The electrical engineering analysis necessary to design these systems is complex as well. In particular, the main areas of concern are:

- Relaying/Controls – scheme and setting of relays.
- Short Circuit Analysis – this is crucial to the operation and durability of the equipment.

Additionally, all architectural and engineering disciplines have their respective design nuances such as:

- Sound
- Stack Height (Air Permitting and Aesthetic Considerations)
- Existing Site Condition Evaluation
- General Architectural Aesthetics
- Effluent Discharge Chemistry and Quantity

Combined Cycle Plant Configuration and Operation

Figure 7 depicts a simplified combined – cycle plant configuration. Cogeneration system operation generally falls into

one of two primary categories:

- Topping Cycle Operation – this operation considers the generation of electric power to be of priority and heat recovery from the process to be of secondary priority. The system controls will ensure that the proper level of power output along with the proper voltage and frequency are maintained. The heat generated in the process is recovered or rejected as needed.
- Bottoming Cycle Operation – this operation considers the generation of thermal heat to be of primary concern and that the electric power generated is of secondary concern. The system controls generally regulate the level of heat generated and consequently the thermal distribution required of the system including steam quality and pressure (or HTHW). If excess [electric] power is generated during the bottoming cycle operation, the power may be exported to the electric utility grid or the combustion turbine controls may throttle back on turbine power generation and increase duct firing for additional heat. There are many scenarios that should be considered before a control scheme is settled upon which are often contingent on the nature of the Interconnect Agreement made with the utility company.

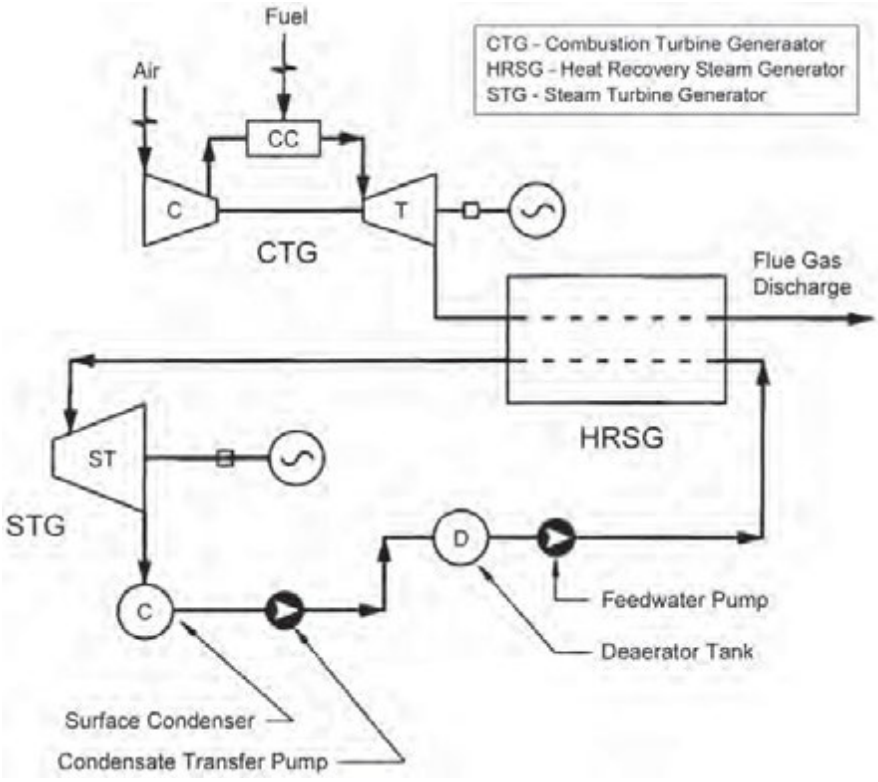


Figure 7. Simplified combined – cycle plant configuration.

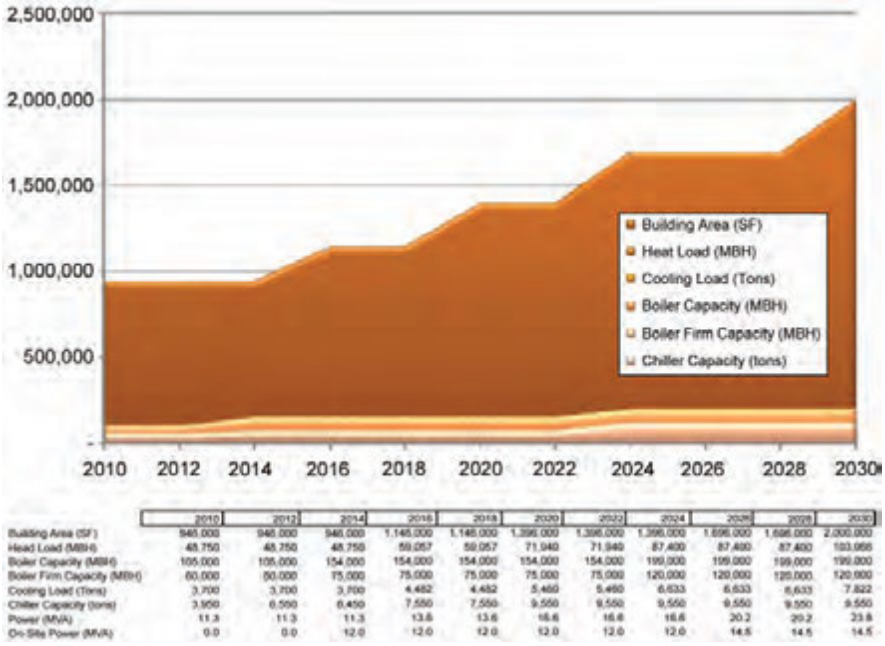
Although the system control priority and details of operation may vary, the overall operation of the system is similar. The general sequence is as follows:

- The CTG is engaged by firing either natural gas or No.2 fuel oil. The hot gasses expand out of the turbine creating mechanical work and thus, electric power. The actual [hot flue] discharge gases from the turbine are then supplied to a Heat Recovery Steam Generator (HRSG).
- The HRSG generates steam (via the hot flue gas) that is in turn supplied to a steam turbine. The steam enthalpy drop across the turbine is transmitted into an enhanced work that may be used to generate electric power or be utilized for process steam distribution.
- The steam discharge from the turbine is either in a condensed form (accomplished with cooling tower water and vacuum pumps) and collected in a storage/receiver tank, or steam at a lower pressure that may be utilized for heating or process purposes.
- This collected water is then pumped to a deaeration vessel that preheats the water and removes free oxygen from the water. This water is then pumped into the HRSG and the cycle repeats.

Combined Cycle Congeneration Plant
Environmental Technology

One of the most significant issues that affects the feasibility of cogeneration projects is the amount of emission control equipment needed for a particular application. Emissions control devices are applied to various components of the system in order to remove contaminants, such as Nitric Oxide Compounds (NOx), Sulfur Oxide compounds (Sox), Carbon Monoxide (CO) and Volatile Organic Compounds (VOC's). The level of emissions removal is usually determined by the Federal and State Environmental Regulations. The following are commonly utilized emissions reduction equipment in cogenerative systems:

- Selective Catalytic Reduction (SCR) – ammonia is sprayed into the flue gas stream across a catalyst in order to discharge air, water and minor emissions.
- NOx Spray – purified water is sprayed into the combustion chamber of a CTG to lower the flame temperature and reduce the generation of NOx emissions.



	2010	2012	2014	2016	2018	2020	2022	2024	2026	2028	2030
Building Area (SF)	946,000	946,000	946,000	1,146,000	1,146,000	1,396,000	1,396,000	1,396,000	1,696,000	1,696,000	2,000,000
Heat Load (MBH)	48,750	48,750	48,750	59,057	59,057	71,940	71,940	87,400	87,400	87,400	103,068
Boiler Capacity (MBH)	105,000	105,000	154,000	154,000	154,000	154,000	154,000	199,000	199,000	199,000	199,000
Boiler Firm Capacity (MBH)	60,000	60,000	75,000	75,000	75,000	75,000	75,000	120,000	120,000	120,000	120,000
Cooling Load (Tons)	3,700	3,700	3,700	4,482	4,482	5,460	5,460	6,633	6,633	6,633	7,822
Chiller Capacity (tons)	3,950	6,550	6,450	7,550	7,550	9,550	9,550	9,550	9,550	9,550	9,550
Power (MVA)	11.3	11.3	11.3	13.6	13.6	16.6	16.6	16.6	20.2	20.2	23.8
On-Site Power (MVA)	0.0	0.0	12.0	12.0	12.0	12.0	12.0	12.0	14.5	14.5	14.5

Figure 8. Facility energy load profile projections.

- Dry-Lo NOx Combustion –the flame temperature is staged during combustion to keep the flame temperature below the level of high NOx generation.
- Urea Spray – similar process to the SCR ammonia process.

Once an Environmental Impact Study and an Air Permit Application is developed, the appropriate technology should be selected. Upon generating more than a certain level of fuel usage and/or emissions, Continuous Emissions Monitoring Systems (CFMS) are required to monitor the plant emissions year round. These devices are intended to document and prove that the systems are operating in a manner similar to what they were permitted for. These issues are determined when Air Permits are developed early on during the project. This equipment does not only have an equipment capital cost impact, but also a space impact and operational cost. These factors need to be considered in the Feasibility Study Phase of the work.

Total Energy Plant (TEP) Configuration

Cogeneration plants are often configured so that they can be integrated into central cooling systems that utilize heat to provide cooling (i.e., absorption cooling). Surplus heat rejected from the cogeneration process during summer months may be utilized for the creation of steam for absorption chilling. This often has the effect of "flattening" the campus steam load profile providing for more optimum equipment selection and efficient operation.

Cogeneration – A Business Case Perspective

Without a sound business financial basis, the positive technical attributes of cogeneration/CHP would not be potentially as attractive. The primary reason most businesses invest money in aspects of their business is to make or save money. When all is said and done, the application of cogeneration must be economically beneficial. In order to determine this, a series of steps is typically followed to reach an economic justification for the project.

The first step in the business/financial investigation is to perform a Cogeneration Screening Analysis. This is intended to be a brief study to determine if implementing Cogeneration/CHP is worthy of consideration. Very high natural gas prices and low cost/high reliability utility power can quickly dissuade an owner from wanting to pursue generating on-site power.

Another consideration common to pharmaceutical facilities is planning for future growth. The development of an "Energy Master Plan" to "track" a "Site Master Plan" that includes load profiles for electric power consumption, heating load, and cooling load is customarily performed.

Data and calculations for each of these parameters are easily put into a spreadsheet format that can then be converted into graphical form, as seen in Figure 8.

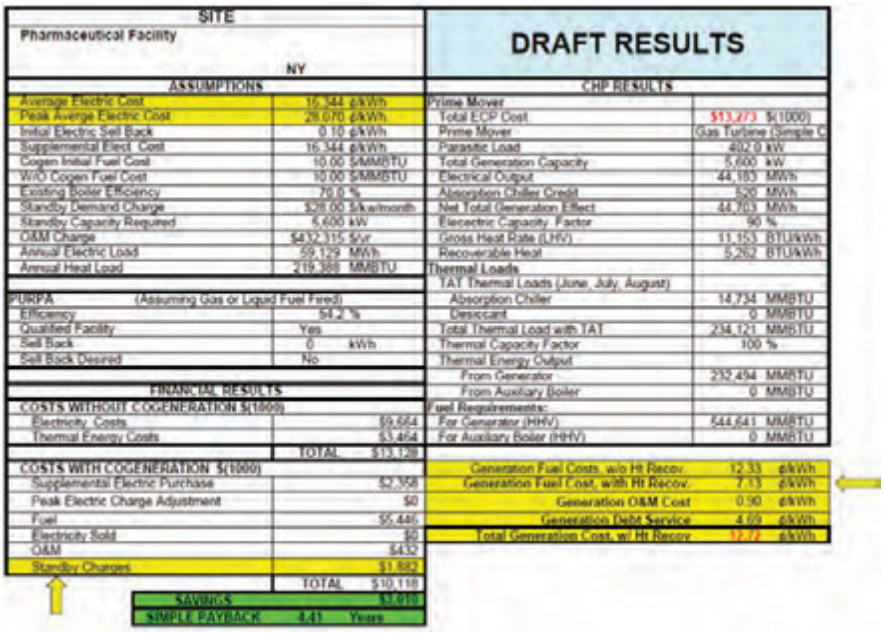
The Screening/Analysis/Business Case decision making process generally considers several issues:

- Capital Costs for Construction
- Operational Maintenance Costs
- Energy Costs (Fuel, Electric Power, etc.)
- Project Delivery Considerations
- Financing Methods
- Ownership and Risk Assessment
- Sensitivity Analysis

The Screening Analysis should be issued in the form of a report that has narrative explanatory information with the data and calculations. The narratives should include Conclusions, Recommendations and overall Summary.

Financial Issues

As previously stated, the implementation of cogeneration projects is considered primarily for economic reasons. Although there are occasional circumstances where an owner wants to own its power generating system or the electric grid serving an energy user may be unreliable (i.e., frequent



SITE		DRAFT RESULTS	
Pharmaceutical Facility			
NY			
ASSUMPTIONS		CHP RESULTS	
Average Electric Cost	16.344 ¢/kWh	Prime Mover	
Peak Averge Electric Cost	28.070 ¢/kWh	Total ECP Cost	$13,273 $(1000)
Initial Electric Sell Back	0.10 ¢/kWh	Prime Mover	Gas Turbine (Simple C
Supplemental Elect. Cost	16.344 ¢/kWh	Parasitic Load	402.0 kW
Cogen Initial Fuel Cost	10.00 $/MMBTU	Total Generation Capacity	5,600 kW
W/O Cogen Fuel Cost	10.00 $/MMBTU	Electrical Output	44,183 MWh
Existing Boiler Efficiency	70.0 %	Absorption Chiller Credit	520 MWh
Standby Demand Charge	$28.00 $/kw/month	Net Total Generation Effect	44,703 MWh
Standby Capacity Required	5,600 kW	Elecectric Capacity Factor	90 %
O&M Charge	$432,315 $/yr	Gross Heat Rate (LHV)	11,153 BTU/kWh
Annual Electric Load	59,129 MWh	Recoverable Heat	5,262 BTU/kWh
Annual Heat Load	219,368 MMBTU	Thermal Loads	
		TAT Thermal Loads (June, July, August)	
PURPA (Assuming Gas or Liquid Fuel Fired)		Absorption Chiller	14,734 MMBTU
Efficiency	54.2 %	Desiccant	0 MMBTU
Qualified Facility	Yes	Total Thermal Load with TAT	234,121 MMBTU
Sell Back	0 kWh	Thermal Capacity Factor	100 %
Sell Back Desired	No	Thermal Energy Output	
		From Generator	232,494 MMBTU
FINANCIAL RESULTS		From Auxiliary Boiler	0 MMBTU
COSTS WITHOUT COGENERATION $(1000)		Fuel Requirements:	
Electricity Costs	$9,664	For Generator (HHV)	544,641 MMBTU
Thermal Energy Costs	$3,464	For Auxiliary Boiler (HHV)	0 MMBTU
TOTAL	$13,128		
COSTS WITH COGENERATION $(1000)		Generation Fuel Costs, w/o Ht Recov	12.33 ¢/kWh
Supplemental Electric Purchase	$2,358	Generation Fuel Cost, with Ht Recov.	7.13 ¢/kWh
Peak Electric Charge Adjustment	$0	Generation O&M Cost	0.90 ¢/kWh
Fuel	$5,445	Generation Debt Service	4.69 ¢/kWh
Electricity Sold	$0	Total Generation Cost, w/ Ht Recov	12.72 ¢/kWh
O&M	$432		
Standby Charges	$1,882		
TOTAL	$10,118		
SAVINGS	$3,010		
SIMPLE PAYBACK	4.41 Years		

Figure 9. Screening analysis results.

voltage drops, poor power quality, frequent black-outs), historically it was the norm that the decision to provide on-site power was based on financial benefits. During periods when electric power costs are high and fossil fuel costs are low, cogeneration tends to be a more attractive alternative. Environmental legislation has become a very significant element that has now become a major factor in the decision making process.

When considering cogeneration, a complete economic analysis is customarily performed that accounts for the following:

- Electric Utility Rates (both Energy and Demand Charges)
- Utility Grid Interconnection Costs
- Standby Interconnection Costs
- Fuel Costs
- Equipment Capital Costs
- Cost of Construction and Soft Costs
- O&M Costs
- Cost of Money
- Utility Rebates and Public Incentive Funding Opportunities

Load profiles of the facility in question are documented in terms of peak load, energy consumption and their respective time periods. The cost of a new cogeneration system is compared with the utility grid cost from an LCC (Life Cycle Cost) perspective, and then an economic determination is made. If the economic benefits are apparent and the owner is committed to cogeneration, typically the project is initiated.

Capital Cost for Construction

The equipment, system and building elements needed to construct a cogeneration system/facility have substantial costs that need to be considered. Along with these costs are the cost considerations involved with running a parallel operation with the utility company. A preliminary screening analysis will often use "rule of thumb" building and system costs; however, if a detailed business case analysis is being performed, the capital cost estimates should be based upon schematic documents and vendor equipment quotes for reliable accuracy.

Operational and Maintenance Costs

These costs include labor rates, union issues, cost of spare parts and tools, warranty issues, etc.

Cost of Energy (Fuel, Electric Power, etc.)

Both the cost of electric power (from the local utility provider) and natural gas are critical not only from a present period cost, but even more so from a long term perspective. When computing these costs, it is vital to consider the long term costs of these commodities as well as current prices. Currently, it is believed that natural gas prices (according to the US Energy Information Agency (USEIA)) should be flat and likely decline slightly over the next 10 years. Electric power (grid) rates are projected to rise slightly over that time.

Project Delivery Considerations

Many different methods can be employed when constructing and operating cogeneration facilities, but summarized below for design/bid/build consideration are the three primary methods:

- Traditional Design/Bid/Build (Owner-Owned Operate – Option 1)

In this option, all aspects of the system are the responsibility of the owner, including performance, reliability, financing and price risk on natural gas procurement. It is assumed that the facilities would be constructed using typical design-build procurement; therefore, the owner would assume all price risk. All responsibility for the operations, maintenance, and possible regulatory matters also would be borne by owner.

- Design-Build/EPC Contractor (Owner Own/Third Party Construct and Operate – Option 2)

This option considers the owner owning the CUP with cogeneration; however, all operations would be outsourced to an ISP. The facilities could be constructed by either the owner or the ISP, with financing provided by the owner. The ISP would be responsible for performance and reliability of the system, likely including a performance guarantee. Price and demand risk would likely be a responsibility shared by both parties.

- DEBOOT – (Design/Build/Own/Operate/Transfer (Owner Purchase Energy/Third Party Own and Operate as an Energy Provider – Option 3)

In this third option, the Central Utility Plant (CUP) with cogeneration would be owned by the ISP and operated by the ISP. The facility owner would likely have to sub-divide the property on which the CUP is constructed and lease the land to the ISP with a long-term land lease. The CUP facility would be designed, constructed and financed by the ISP, thereby relieving pharmaceutical facility owner of all risks related to design and construction. The ISP also would be responsible for performance and reliability of the system, likely via a performance guarantee. As with Option 2, responsibility for price and demand would likely be shared by both parties.

Each of the individual options has different characteristics and differing levels of risk and liability. (The "Base Case" defines the plant without cogeneration including a central boiler and chiller plant and utility substation power). The Business Case Analysis Quantitative Calculations are summarized in Table A.

As seen above, there is considerable difference in the evaluations depending on whether actual or discounted dollars are used and also notice the small cost increase relative to having the ability to off-load the responsibility of providing energy to a third party (However, this varies for every project).

Sensitivity Analysis

A particularly useful form of analysis is one referred to as a Sensitivity Analysis. This analysis adjusted the values of certain variables being examined in order to ascertain the potential economic levels of volatility.

Many assumptions were required to prepare financial forecasts for the options. Because variations in these assumptions are inevitable, a sensitivity analysis has been prepared on the key assumptions that will have the greatest impact on the overall results. This analysis is provided in Table B.

Central Utilities Project								
Summary of Options	Estimated Total Costs to Proposed Facility							
	Net Present Value @ 6.5%				Actual Dollars			
Cost Statement	Base	Option 1	Option 2	Option 3 ISP/ISP	Base	Option 1	Option 2	Option 3 ISP/ISP
Operations and maintenance expense	20,751,062	25,604,189	25,604,189	25,604,189	46,345,996	57,185,105	57,185,105	57,185,105
Less: ISP efficiency credit	na	na	(2,304,377)	(2,304,377)	na	na	(5,146,659)	(5,146,659)
Fuel purchases	53,128,403	86,645,814	86,645,814	86,645,814	134,055,105	207,870,498	207,870,498	207,870,498
Electricity purchases	147,751,877	62,219,610	62,219,610	62,219,610	364,041,684	167,761,567	167,761,567	167,761,567
Amortization expense	17,699,162	21,649,256	21,649,256	26,741,060	38,708,512	47,283,055	47,283,055	55,092,589
Interest expense	na	na	na	15,083,075	53,607,300	65,606,658	65,606,658	28,507,030
Income tax expense	na	na	na	12,588,787	na	na	na	27,157,196
ISP return on rate base (after tax)	na	na	na	35,055,536	na	na	na	75,651,501
Total Cost	239,330,505	196,118,869	193,814,492	261,633,693	636,758,597	545,706,884	540,560,224	614,088,827
Cash Flows Inflow (Outflow)				Not applicable to Option 3				Not applicable to Option 3
From Operations								
Net cost	(267,530,541)	(230,521,005)	(228,216,628)		(636,758,597)	(545,706,884)	(540,560,224)	
Add: Amortization expense	17,699,162	21,649,256	21.649,256		38,708,512	47,283,055	47,283,055	
From Investing								
Construction: plant & distribution – steam/chillers	(41,930,933)	(41,930,933)	(41,930,933)		(47,758,597)	(545,706,884)	(540,560,224)	
Construction: plant & distribution – cogen	na	(12,182,042)	(12,182,042)		na	(13,811,079)	(13,811,079)	
Construction - buildings	(10,420,236)	(10,420,236)	(10,420,236)		((11,378,647)	(11,378,647)	(11,378,647)	
Capital renewal – steam/chillers	(10,748,090)	(10,748,090)	(10,748,090)		(27,161,083)	(27,161,083)	(27,161,083)	
Capital renewal - cogen	na	(2,718,414)	(2,718,414)		na	(6,869,600)	(6,869,600)	
Capital renewal – buildings	(3,020,151)	(3,020,151)	(3,020,151)		(7,632,106)	(7,632,106)	(7,632,106)	
Net Cash Flow (20 years operations)	(315,950,789)	(289,891,615)	(287,587,237)	(261,633,693)	(691,760,043)	(612,814,466)	(607,667,806)	(614,088,827)
Asset purchase from ISP after Year 20	na	na	na	(10,912,005)	na	na	na	(46,445,702)
Total Project Net Cash Flow	(315,950,789)	(289,891,615)	(287,545,698)	(272,545,698)	(691,760,043)	(612,814,466)	(607,667,806)	(660,534,529)
Ranking:	4	3	2	1	4	2	1	3

Table A. Business case analysis quantative calculations.

This Sensitivity Analysis adjusts the costs of electricity and natural gas considering projected inflation levels and their impact on the various project delivery methods.

Carbon Footprint Reduction Potential

Environmental concerns are gradually increasing so that today private and public sector individuals and organizations have a common goal to minimize the impact of emissions on the environment. These concerns range from emissions that result in "acid rain" to "global warming." The employment of cogeneration/CUP has the added benefit of almost universally decreasing the "carbon footprint" of the area in which the system is located.

The carbon footprint of a facility is defined as the "direct and indirect effect that individual and corporate actions have on the environment in terms of Carbon Dioxide (CO_2) emissions." Legislation is developing to include Greenhouse Gases (GHG) into the Clean Air Act and require emissions reporting. Methods for determining carbon footprint status have been developed that can assist individuals and companies in determining these values.

Since cogeneration systems operate at greater efficiencies than typical large scale fossil fuel power generating stations, the ability to lower the overall carbon footprint of a region can be decreased. If the less efficient power station does not have to provide power for facilities with cogeneration (or supplement with less power), then the power station burns less fuel, thus lowering the overall Co_2 (among others) emissions in that locality.

Calculating a Carbon Footprint

A carbon footprint can be derived by calculating direct and indirect GHG emissions. Greenhouse gases include carbon dioxide (CO_2), nitrous oxide (N_2O), methane (CH_4), hydrofluorocarbons (HFCs), perfluorocarbons (PFCs), and sulfur hexafluoride (SF_6). The total amount of greenhouse gases from direct and indirect emissions are expressed in equivalent tons of CO_2. The greenhouse gases are converted into a uniform measure designated in carbon or carbon dioxide equivalents (CO_{2e}) based on Global Warming Potentials (GWPs). GWPs are used to compare the abilities of the different greenhouse gases to trap heat in the atmosphere and are based on the heat-absorbing ability of each gas relative to that of CO_2.

Based on the Second Assessment Report (SAR) of the Intergovernmental Panel on Climate Change (IPCC, 2001), one metric ton of N_2O is equal to 310 metric tons of CO_{2e} and one metric ton of CH_4 is equal to 21 metric tons of CO_{2e}.

Per the Climate Registry GRP, greenhouse gas emissions are categorized into three separate scopes, which are described below:

- Scope 1 – Direct Emissions: emissions from on-site stationary fuel combustion sources, mobile sources that are owned and operated by the facility such as vehicles and/or fleets, and direct fugitive emissions from refrigerants
- Scope 2 – Indirect Emissions: electricity consumption, imported steam, and purchased heating
- Scope 3 – Indirect Emissions: all other indirect emissions such as purchased materials, employee travel, etc. These are not widely accepted emissions values

Central Utilities Plant Project					
Sensitivity Analysis		20 Year Total Cost – 6.5% NPV			
		Base Case	Option 1 Owner/Owner	Option 2 Owner/ISP	Option 3 ISP/ISP
Report Rankings	$	(315,950,789)	(289,891,615)	(287,587,237)	(272,545,698)
	Rank	4	3	2	1
Energy Forecasts per the U.S. Energy Administration Institute					
Natural Gas only (2.16%)	$	(307,860,262)	(277,595,733)	(275,291,356)	(260,122,010)
(Assumption = 4.4%)	Rank	4	3	2	1
Electricity only (0.28%)	$	(285,894,756)	(275,739,809)	(273,435,432)	(258,248,228)
(Assumption = 2.7%)	Rank	4	3	2	1
Both Natural Gas and Electricity	$	(277,804,229)	(263,443,927)	(261,139,550)	(245,824,540)
	Rank	4	3	2	1
Interest Rate – ISP Loan					
Break Point Rate (6.875%) = the interest rate where Option 3 loses advantage				(287,587,237)	(287,739,846)
ISP After-tax ROE					
(Assumption = 10.5%)					
Break Point ROE (15.85%) = the ROE where Option 3 loses advantage				(287,587,237)	(287,692,497)
ISP Efficiency Gains					
(Assumption = 9.0%)					
Zero (0%)	$	(315,950,789)	(289,891,615)	(289,891,615)	(284,622,008)
	Rank	4	3	2	1

Table B. Sensitivity analysis.

SCOPE 1 DIRECT EMISSIONS (STATIONARY AND MOBILE FUEL COMBUSTION AND REFRIGERANT LOSS) AND SCOPE 2 INDIRECT EMISSIONS (PURCHASED ELECTRICITY AND STEAM)															
BUILDING	BUILDING AREA (s.f.)	UNITS (No.)	2009 AVE. TEMP. (°F)	2009 ELECTRICITY USAGE (kwh)	2009 ELECTRICITY USAGE PER BUILDING AREA (kwh/s.f.)	2009 NATURAL GAS USAGE (therms)	2009 FUEL OIL USAGE (gallons)	2009 AUTO GAS & DIESEL (gallons)	2009 APPROX. REFRIGERANT LOSS (lbs)	SCOPE 1 EMISSIONS (STATIONARY & MOBILE COMBUSTION SOURCES, AND REFRIGERANTS) (metric tons of CO_{2e})	SCOPE 2 EMISSIONS (PURCHASED ELECTRICITY, HEATING AND COOLING) (metric tons of CO_{2e})	TOTAL CARBON FOOTPRINT- SCOPE 1 & 2 EMISSIONS (metric tons of CO_{2e})	TOTAL CARBON FOOTPRINT PER OPERATING HOSPITAL BED (metric tons of CO_{2e}/bed)	TOTAL CARBON FOOTPRINT PER BUILDING AREA (metric tons of CO_{2e}/s.f.)	TOTAL CARBON FOOTPRINT PER BUILDING AREA (lbs of CO_{2e}/s.f.)
1	190,934	312	53.0	6,163,200	32.3	441,317	10,502	139	324	2,712	2,286	4,998	16.0	0.03	57.7
2	204,957	305	53.2	7,311,000	35.7	335,301	4,031	8,595	234	2,011	5,122	7,133	23.4	0.03	76.7
3	371,281	265	52.3	8,751,420	23.6	496,482	1,062	603	195	2,812	6,131	8,944	33.7	0.02	53.1
4	409,000	408	52.1	11,232,520	27.5	789,677	3,000	1,101	390	4,586	7,870	12,456	30.5	0.03	67.2
5	873,000	652	55.5	29,384,984	33.7	131,605 Mbs purchased- Scope 2	16,350	0	24	187	21,067	21,254	32.6	0.02	53.7
6	230,000	0	55.5	6,107,743	26.6	36,599 Mbs purchased- Scope 2	399	0	0	4	5,093	5,097	NA	0.02	48.9
7	936,211	644	53.0	34,516,080	36.9	2,950,624	109,288	15,363	171	17,097	12,803	29,900	46.4	0.03	70.4
8	946,434	812	53.0	28,284,080	29.9	2,979,467	15,349	22,823	133	16,325	19,816	36,141	44.5	0.04	84.2
9	562,200	0	53.0	11,602,180	20.6	661,053	212,595	0	500	6,146	8,128	14,275	NA	0.03	56.0
10	168,481	204	53.3	6,195,680	36.8	273,078	2,247	488	432	1,825	4,341	6,166	30.2	0.04	80.7
11	407,647	341	53.8	12,192,660	29.9	863,322	3,000	2,314	900	4,671	8,542	13,213	38.7	0.03	71.5
12	736,203	508	52.2	20,191,200	27.4	1,309,580	30,000	10,969	70	7,422	7,490	14,911	29.4	0.02	44.7
13	258,924	206	52.2	5,019,600	19.4	770,080	6,500	582	400	4,487	1,862	6,349	30.8	0.02	54.1
14	118,351	103	52.4	5,752,800	48.6	279,291	668	2,589	0	1,557	4,030	5,587	54.2	0.05	104.1
15	260,117	236	53.0	2,529,600	9.7	22,219	144,169	6,382	175	1,891	938	2,830	12.0	0.01	24.0
TOTALS	BUILDING AREA (s.f.)	OPERATING HOSPITAL BEDS (No.)	AVE TEMP. (°F)	ELECTRICITY USAGE (kwh)	ELECTRICITY USAGE PER BUILDING AREA (kwh/s.f.)	NATURAL GAS USAGE (therms)	FUEL OIL USAGE (gallons)	AUTO GAS & DIESEL (gallons)	APPROX. REFRIGERANT LOSS (lbs)	SCOPE 1 EMISSIONS (STATIONARY & MOBILE COMBUSTION SOURCES, AND REFRIGERANTS) (metric tons of CO_{2e})	SCOPE 2 EMISSIONS (PURCHASED) ELECTRICITY, HEATING AND COOLING) (metric tons of CO_{2e})	TOTAL CARBON FOOTPRINT SCOPE 1 & 2 EMISSIONS (metric tons of CO_{2e})	AVERAGE CARBON FOOTPRINT PER OPERATING HOSPITAL BED (metric tons of CO_{2e}/bed)	AVERAGE CARBON FOOTPRINT PER BUILDING AREA (metric tons of CO_{2e}/s.f.)	AVERAGE CARBON FOOTPRINT PER BUILDING AREA (lbs of CO_{2e}/s.f.)
	6,673,740	4,996	53.2	195,234,747	29.2	12,171,491	559,160	71,949	3,948	73,736	115,520	189,255	33	0.03	63

Figure 10. 2009 carbon footprint analysis – scope 1 direct emissions and scope 2 indirect emissions.

Figure 10 depicts the carbon footprint of various sites of an owner in the state of New York. Cogeneration can often lower carbon dioxide emissions at one site that may be used as credits to increase CO_2 emissions at another site (thus allowing building/facility expansion or provide carbon credits that can be traded to other businesses).

Conclusion

Cogeneration systems have been popular in the last 30 years for the production of electric power and useful heat. The greater improved cycle efficiencies, when compared to the traditional Rankine-Regenerative, have made them grow in popularity from an economic and environmental perspective. Most combustion turbine generator sets fire natural gas as the primary fuel, which is the most environmentally friendly fossil fuel (in terms of the generation of emissions) that can provide year-round reliable heat and cooling for pharmaceutical production and research facilities. The systems have been employed in applications ranging from 2 MW college campuses to 750 MW merchant power plants. Cogeneration projects require study and analysis from the feasibility stage through the detailed design phases and construction of the project. The analysis of economic, regulatory and technical issues requires considerable attention, as does the ability to work cooperatively with owners and regulatory authorities. When these issues are properly addressed, cogeneration may be a viable option that could improve the operation, economics and environmental status of a client and of society in general.

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A Practical Approach to Managing Knowledge – A Case Study of the Evolution of Knowledge Management (KM) at Merck

by Marty Lipa, Samantha Bruno, Michael Thien, ScD, and Robert Guenard, PhD

This case study presents the development of a knowledge management program, including the creation of a strategy, a suite of capabilities and model for sustaining the flow of knowledge, and establishing and maintaining the connection to improved business outcomes.

One of the most important "products" in today's businesses is *knowledge*. It is experience and expertise. It is what we know about products and processes. It is rationale behind decisions. It informs risk-based decisions. It is know-how and know-*why*. According to Drucker,[1] "The basic economic resource – the means of production – is no longer capital, nor natural resources, nor labor. It is and will be knowledge." One of the premier knowledge management organizations, the American Productivity and Quality Center (APQC) suggests that "Everyone competes on how much they know."[2] As Fred Miller from Kaleel Jamison Consulting Group states, "The main competitive advantage organizations now have is the ability to transfer and apply knowledge."[3] Yet, knowledge is seldom treated like a crucial asset. With the right approach, companies can leverage knowledge management (KM) to drive critical business outcomes, such as improved customer service and quality, financial and operating benefits, and higher employee engagement.

So what is knowledge management? From a practical perspective, *knowledge* is information in action. *Until people take information and use it, it isn't knowledge.*[2] Further, *knowledge management* is a systematic effort to enable information and knowledge to grow, flow and create value.[2]

Knowledge is a critical product – a crucial asset – in all industries, and the pharmaceutical, biotech and related sectors are no exception. For example, consider the development cycle of pharmaceutical products. The physical value of the clinical supplies is insignificant compared to the knowledge that has been compiled about the mechanism, molecule, and means to manufacture. Every day knowledge workers seek, share and leverage knowledge to develop, support and manufacture products.

Current trends further highlight the importance of an emerging expectation for managing knowledge in the pharmaceutical sector. The recently published International Conference on Harmonisation (ICH) guidelines which establish the paradigm for Quality by Design and development and manufacture of drug substances, specifically ICH Q8 (R2) *Pharmaceutical Development*,[4] ICH Q9 *Quality Risk Management*,[5] ICH Q10 *Pharmaceutical Quality System*,[6] and ICH Q11 *Development and Manufacture of Drug Substances*[7] establish knowledge management as an enabler

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Figure 1. ICH Q10 Pharmaceutical Quality System Model.

of the entire lifecycle of a pharmaceutical product - *Figure 1.* Q10 defines knowledge management similar to APQC as a "Systematic approach to acquiring, analyzing, storing, and disseminating information related to products, manufacturing processes and components."

So the need to manage knowledge is clear, but what does this mean in practice? Where to focus? Where to start, and how? This article will present a practical approach to knowledge management by way of a case study at Merck, showcasing the development of a KM Program including the creation of a strategy for managing knowledge, a suite of business capabilities and support model for sustaining the flow of knowledge, and establishing and maintaining the connection to improved business outcomes.

Origin of the KM Journey for Merck Global Science, Technology and Commercialization

The Global Science, Technology and Commercialization (GSTC) function at Merck performs late stage product development, launch and ongoing technical support of the manufacture of all pharmaceutical products. GSTC also provides manufacturing operations for clinical studies and commercial supply. The function is comprised of approximately 3000 highly skilled scientists, engineers, technicians, and support persons who are dispersed in more than 50 locations and 20 countries around the globe.

In addition to the typical challenges of operating a large, global, knowledge-rich business that is highly dynamic and undergoing unprecedented change due to a multitude of internal and external trends, the following key factors were converging in 2008 and 2009:

- Anecdotal evidence pointed to the opportunity to better leverage knowledge across the product life-cycle. Experiences included difficult technology transfers of products between manufacturing sites; difficulties in finding information for routine business operations such as problem solving and investigations; inefficiencies and missed business opportunities for how products were developed and filed; and missed opportunities to capture critical insights and expertise gained from years of experience from highly knowledgeable experts leaving or retiring from the Company.
- The paradigm for Quality by Design (QbD)[4,5,6] was emerging and Merck recently had first-hand experience as a participant in the Food and Drug Administration Center for Drug Evaluation and Research Chemistry, Manufacturing, and Controls Pilot Program where firms worked closely with the Agency reviewers to build in a QbD approach on an actual New Drug Application. QbD presented a new perspective for the opportunity to leverage "prior knowledge" and the expectation to effectively manage knowledge across the product lifecycle.
- The merger between Merck and Schering-Plough, which was a large and complex integration doubling the size and scope of the company. At this point, even tenured experts knew only a fraction of the expertise available in the new, expanded global organization.
- The growing emergence of the field of knowledge management and awareness of successful practitioners in other industries, as well as change forces such as social computing, expanding demographics (generational differences, pending retirement of baby boomers), and mobility.

These issues pointed to sub-optimal performance, missed opportunities and general "waste" in how knowledge was managed, putting various business objectives at risk. Merck senior management saw an opportunity to secure the value of knowledge as an asset and address these issues. The stage was set – and the first step was to create a strategic plan.

Creation of the Strategic Plan

Strategy development commenced with the following primary objectives:

- **Create Alignment** – Align on the problem and opportunity, increase competency and create a shared mindset for how to think about knowledge management. Ensure direct alignment with broader business direction and outcomes.
- **Set direction** – "Strategy renders choices about what not to do as important as choices about what to do,"[8] and the strategy must define specific objectives and outcomes, the priorities on where to start (including where *not* to focus), a clear vision for the future state and a roadmap of actions to get there.
- **Concentrate resources** – Define and apply what is needed to achieve the strategy, including people, specific skills, financial investment and other resources and capabilities such as change management, training, communications, and information technology.

A Design for Six Sigma (DFSS)[9] approach, specifically the Define-Measure-Analyze-Design-Verify) (DMADV) methodology,[9] was employed to develop the strategy. While not discussed in detail here, the DFSS approach ensured an outcome (i.e., the strategy) that was aligned with stakeholder needs and a line of sight to business strategy; had a baseline measurement established; and had a control plan to measure future effectiveness. APQC was selected as a partner to help teach, coach and advise during strategy development, bringing rich experience in knowledge management and an extensive practitioner network.

Table A depicts a high level description and selected deliverables for each step of the DMADV methodology. Additional discussion on selected activities and deliverables (**bold** in table) follows.

DMADV Steps	Key Activities and Deliverables
Define – What are the goals of improved knowledge management?	• Charter project, establish team • Gather anecdotal evidence, including baseline performance • Assess risk to realization of business strategy
Measure – What knowledge is most important to core work and associated impact?	• Stakeholder input ("voice of business") • Benchmarking (internal and external) • Define specific impact to business strategy
Analyze – How does knowledge currently flow through business processes?	• **Knowledge maps** for target business processes • Gap analysis for high impact opportunities • Business cases
Design – What is future state and what steps to get there?	• Strategic plan, including definition of: - **Strategy principles** - **KM principles** - **KM program** - **Pilot projects** for core capability development • **Roadmap** for KM implementation, including performance targets
Verify – Did the strategy deliver intended outcomes?	• Stakeholder feedback and repeat performance assessment • Establish control and monitoring plan • Measure and sustain

Table A. DMADV for KM strategy overview and selected deliverables.

Knowledge Maps

Knowledge mapping[10] was used as a powerful diagnostic to identify the knowledge requirements for prioritized business processes. During strategy development, knowledge maps as depicted in Figure 2 were used to capture specifically what explicit and tacit knowledge was *required* for a given business process. A subsequent gap analysis, including an impact assessment, clearly identified high-priority, high-impact opportunities to improve knowledge flow.

Principles to Guide Strategy Execution

Principles for the execution of strategy were adapted from APQC models[2] and other perspectives:

- *Align with business process and associated business case:* focus on areas of highest business impact and align KM activities with core business processes.
- *Learn by doing:* partner with appropriate subject matter experts, build for immediate use and optimize in place.
- *Leverage common approaches, processes and platforms:* create standard capabilities to adapt and expand to similar knowledge needs.
- *Measure KM approaches and associated business outcomes:* capture, quantify and communicate direct and indirect benefits of improved knowledge management related to critical business objectives.
- As learned from Charlie Honke and colleagues while at IBM's Fishkill semi-conductor facility (2008), "*think big, start small, but start.*"[11]

Knowledge Management Principles

In addition to strategic principles, a methodology on how to

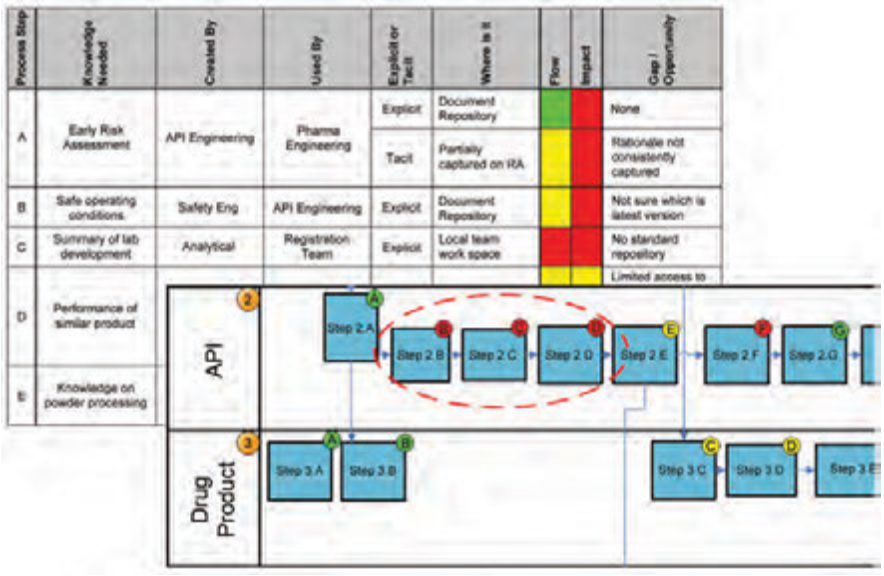

Figure 2. Knowledge map.

approach knowledge management was established. This was adapted largely from APQC[2] framework and learnings during strategy development.

- A majority (~80%) of knowledge is *tacit* (experiences, expertise, insights, etc.) and is not easily captured. Only ~20% is *explicit* (easily documented and transferred). Both are necessary although may be addressed by different tactics.
- Knowledge management is about enabling *knowledge flow*. That is, knowledge flows through a process where knowledge is created, identified, collected, reviewed, shared, accessed and used – and ultimately, reused. Given this mindset, one can begin to discern breakdowns in the *flow* of knowledge.
- Capabilities for managing knowledge need to be embedded "*in the flow*" of business processes. This will change these KM activities from being extra or discretionary to becoming part of how work gets done. Managing knowledge should be a routine, expected and implicit part of daily work.
- Knowledge management capabilities require a holistic approach including *people*, *process*, *content*, and *technology* considerations. *Content* refers to knowledge, but also taxonomies, templates and other supporting elements.

Knowledge Management Program

Models were established for the various elements of governance, as well as teams with the skills required to establish successful knowledge management. This included establishing a dedicated KM Program Office. The KM Program Office was formed to:

Figure 3. Knowledge flow (credit: APQC[2]).

- Educate on best practices based on benchmarking, research and experience
- Facilitate design and implementation of KM capabilities to solve critical business problems
- Lead change management efforts
- Steward, sustain and improve established capabilities
- Create additional capabilities as new opportunities are identified

The roles for the new KM Program Office require a different skillset than the typical scientist or engineer. A typical GSTC employee will have expertise in technical areas such as chemical synthesis or materials characterization, but may not have mastery of the skills required to lead or facilitate such a change to how people work. As such individuals were sought to have skills including strategic/systems thinking, lean six-sigma, change management, facilitation, and project management.

Pilot Projects for Core Capability Development

Prioritization criteria were established based on business impact and aforementioned principles and applied to the completed knowledge maps. A total of four pilot projects were initiated on which to build core capabilities for managing knowledge (described in further detail in the section of this article titled *Core Capabilities: Getting Knowledge to Flow*):

1. *Product knowledge* – knowledge about products and how to manufacture them
2. *Process and Technology Knowledge* – knowledge about core technologies and manufacturing platforms
3. *Connectivity* – Connections to tacit and experiential knowledge involving critical technical topics
4. *Expertise* – Unique technical knowledge held by an individual

Business cases were created to clearly draw the link between improved knowledge flow and the desired business outcomes.

Roadmap for Knowledge Management

A multi-year plan was established, which mapped out the evolution of each KM capability and of the overall KM Program as seen in Figure 4 including target business outcomes. Each capability has a supporting plan that outlines goals for deployment, replication and evolution.

Putting KM Strategy Into Action: Delivering On Strategic Intent

A strongly sponsored, robust strategy anchored around core KM capabilities and supporting KM Program infrastructure positioned the KM Program to begin conducting the initial

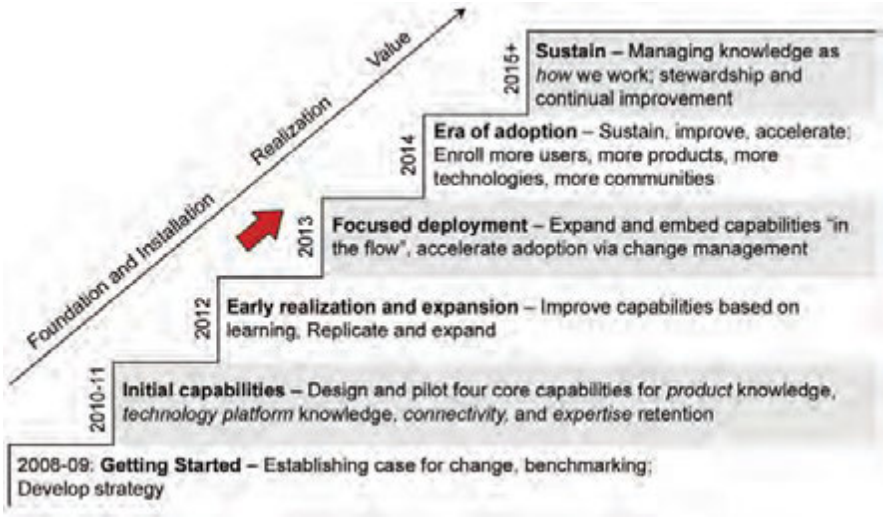

Figure 4. KM roadmap.

capability pilots. The four core capabilities were selected to solve specific knowledge flow gaps in the organization. They also were designed and implemented with long term sustainment, expansion and replication as the ultimate goals. KM could not and would not be another "initiative" which would come and go quickly. In parallel with execution, the guiding principles were applied and through "learning by doing," critical design factors emerged that were common to all capabilities. These factors translated to specific design requirements and a KM solution framework for each capability based upon **P**eople, **P**rocess, **C**ontent, **T**echnology (**PPCT**) – all critical to sustained success. Figure 5 provides an illustrative subset of these requirements.

People and Commitment to Change

Although KM was being led by the KM Program Office in GSTC, all people in GSTC are knowledge workers and managing knowledge is everyone's responsibility. However this was not yet part of the company's culture or designed into business processes or practices. Said differently, there were no expectations for knowledge seeking and sharing behaviors built into how individuals complete their work. The four core capabilities had to include two key things: 1. What individuals would use to help knowledge flow and 2. How they needed to use these core capabilities as part of their "day jobs."

To move beyond installation and achieve full realization of intended outcomes, sustainable shifts need to be achieved in the mindsets and behaviors of a wide range of people. These mindsets and behaviors need to fundamentally change each person's commitment to a new way of thinking and operating. Commitment to change is reflected in the consistency by which the mindsets and behaviors are displayed, even in the face of challenges.[12] These can be addressed though *change management* which is a risk-based change approach to address human aspects of change and increase commitment through targeted actions.

Commitment to change can be visualized as moving targets (people) up a change curve as seen in Figure 6, until internalization of the change[12] is realized.

It is important to determine how to reach the realization tipping point or "the moment of critical mass, the threshold, the boiling point."[13] At this tipping point, KM capabilities are institutionalized, becoming how work is done, and there is no slipping back into the former state. One model for analyzing potential barriers, getting the desired behaviors, and reaching the tipping point is **DCOM**® model.[14] This is a tool to assess what antecedents and consequences are triggering a behavior. From this, one can diagnose what in the environment may need to change in order to realize a change in that behavior. There are four factors that can influence the behavorial change:

- **Direction** – are people directed so the change has the right level of priority/intent?
- **Competence** – do people have the necessary skills?
- **Opportunity** – do people have the time and level of empowerment?
- **Motivation** – what consequences – both positive and negative – are people experiencing? Do they "want to" comply or are they being "forced to" comply?

It was quickly realized that leaders in the organization provide the proper direction, opportunity, and motivation as sponsors for managing knowledge. Without active sponsorship and applied consequences, sustainable change would be difficult if not impossible.

Figure 5. KM solution framework.

Figure 6. Change Commitment Curve adapted from Connor Partners.

Core Capabilities: Getting Knowledge to Flow

The KM Program Office partnered with GSTC technical functions on the design and development of the four initial capabilities. Figure 7 provides a snapshot of the knowledge landscape they cover. The technical functions sponsored specific pilot projects, and provided co-leadership along with the KM Program Office. This created a sense of ownership and accountability for the technical functions. This also created advocates for KM from the bottom up in the organization – which was very powerful when combined with top down sponsorship. The teams utilized the *people, process, content,* and *technology* framework described previously and designed each capability around standard processes. Playbooks were created which allowed each capability to be modular and adaptable for future iterations.

Products: Technical Knowledge (TK)

Intent: Technical knowledge related to a specific Active Pharmaceutical Ingredient (API, or drug substance) or pharmaceutical product (drug product) is readily found and generally accessible by all those who need it at any stage of the product lifecycle. Knowledge associated with changes

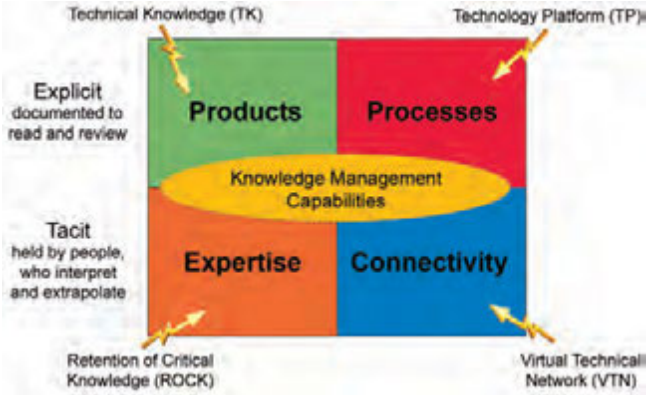

Figure 7. The four core KM capabilities for GSTC.

and experience from testing and manufacturing of a given product is continually captured with context so that it can be used by others. Each project can refer to relevant historical knowledge during development and manufacturing, rather than relying primarily on the personal experience of individuals working on the program.

Description: a unified framework for storage, retrieving, and using product knowledge. The type of technical knowledge in scope is specific to a given product; is generated across the entire lifecycle from development through supply; and encompasses analytical, product and process development, and manufacturing experience. The main elements of this framework are standard content templates to capture knowledge; dedicated stewardship roles; a taxonomy (i.e., classification schema) to tag knowledge; an electronic repository to store knowledge; flexible searching and filtering from multiple business perspectives to find knowledge; and a governance structure to sustain and improve the capability. TK serves as a single access point for the relevant content.

Critical Success Factors:

- **Faceted Taxonomy** providing common language for a diverse set of users
- **Content Stewards** responsible for ensuring product knowledge is kept up to date and knowledge is properly tagged for future retrieval
- **Rationalization of Historical Content** out of hundreds of SharePoint sites, file shares, and other repositories into TK, consolidating to provide a single point of entry for users to find existing information
- **Broad Access** to individuals across the product lifecycle avoiding, "access denied"
- **Search** akin to shopping for products on a website - flexible, easy to refine, and familiar to users

Processes: Technology Platform (TP)

Intent: knowledge related to a specific technology or platform that can be applied across multiple programs is standardized, captured and broadly accessible. The knowledge gained from program experience using a given technology is appropriately captured with context so that it can be reused. Each program incorporates all relevant historical knowledge during development and execution, rather than relying primarily on the personal experience of the individual working on the program.

Description: a Technology Platform is a framework for the capture, storage, maintenance and use/reuse of general knowledge, both tacit and explicit, which applies to a given technology. The type of platform knowledge in scope is generally applicable across multiple programs, including best practices and lessons learned. It encompasses analytical,

process development, equipment, manufacturing science, and operations. The main elements of this framework are a knowledge stewarding Community of Practice (COP) and an electronic repository. The knowledge stewarding business process identifies and captures new general knowledge relevant to the platform and translates lessons learned into best practices.

Critical Success Factors:

- **Relevance of Content** to individuals with a wide range of experience levels (novice to expert)
- **Continuous Growth** of the body of knowledge as new experience is gained on a platform
- **Standardized Look and Feel** across all technology platforms
- **Stewardship** via a COP accountable for sustained knowledge stewardship

Connectivity: Virtual Technical Network (VTN)

Intent: people seeking technical advice and/or access to existing knowledge can efficiently and effectively connect with relevant expertise across the organization. The collective institutional knowledge is harnessed to create business value, enable a more inclusive environment, share best practices, and make problems visible and solve them once.

Description: a professional networking capability for connecting with expertise, enabling discussion and sharing of technical knowledge, anchored in core values held about how people should engage and interact with one another. This capability is comprised of expertise profiles and technical topic communities of practice. The communities are centered on mission-critical technical topics with a direct tie to desired business outcomes. Their main purpose is to serve as a "helping community" for solving problems, but also serve as a place for best practice sharing and innovation.[15] There is no limitation on membership and there are designated stewards to serve as knowledge brokers and sponsors as topic champions.

Using **Inclusion as the *HOW***,®[16] a focus for the manufacturing division, provided a platform for the behavioral elements of the framework. Inclusive behaviors enable people to have a sense of belonging; to feel respected, valued, and seen for who they are as individuals; and a level of supportive energy and commitment from leaders, colleagues, and others so that people – individually and collectively – can do their best work.[16] Energy is a primary determinant of whom we seek out and learn from,[17] and having an inclusive work culture creates that energy in the social space to unleash the knowledge and creativity of people. Further details on this work are reviewed in a related case study.[18]

Critical Success Factors:

- **Dedicated Roles** reflected in annual objectives of community stewards and community sponsors
- **Community Stewards** with the proper skills to be effective knowledge brokers, encouraging and nurturing interaction on their communities
- **Business Focused Topics** determined by business impact/urgency, potential audience/demand, and how well knowledge flows around the topic
- **Success Stories** communicating value and creating relevance for users to reinforce adoption

Expertise: Retention of Critical Knowledge (ROCK)

Intent: knowledge is captured from people who have developed unique technical expertise through challenging and technically complex work and/or through years of experience.

Description: a structured interview process designed to transfer critical knowledge from experts or specialists to others in the organization such that the knowledge can be retained and reused. Criteria are applied to determine the knowledge most critical to the ongoing work in the organization. It may be useful in cases where experts with valuable, unique, and difficult to replicate knowledge transfer, retire or other depart from the company. This practice was developed based on insightful benchmarking discussions with Royal Dutch Shell in 2009 (Donna Hendrix).

Critical Success Factors:

- **Focused Scope** around priority topics and knowledge unique to that individual
- **Standard Work and Facilitation** of the interviews to ask right questions and cover proper scope
- **Sponsorship and Ownership** of the process and the resulting outputs for action

Progress to Date

The initial pilot projects have completed for each KM capability and successfully demonstrated improved knowledge flow through enhanced global collaboration, faster problem solving, improved project execution, and other outcomes. These capabilities are now in "production" use, and are being deployed to more users and teams, more products and technologies, and more functions within the company. The journey is still in its early stages, but results are positive and the future is very promising. Realization of managing knowledge better has already started, with many success stories reported, capturing the value. Success stories include proactive resolution of manufacturing issues, leveraging the global Merck network to more quickly tackle difficult problems, more effective and faster employee onboarding, and more. As anticipated, this value has come in the form of financial, quality, employee engagement and other – often unexpected – benefits.

Key Lessons in Execution

The KM Strategy proved invaluable in establishing purpose, principles and direction for managing knowledge. During strategy execution, several key lessons emerged which are critical to future success.

a. **Alignment with business priorities** and measuring in terms of current metrics is critical to get the attention of leaders and demonstrate value in what matters. It is about helping people do what they already need to do, but better. The sooner value can be established, the sooner the transition will occur from "knowledge management as an initiative" to "managing knowledge as how work gets done."
b. **Sponsorship, Sponsorship, Sponsorship** – sponsors are the individuals that can legitimize a change and provide meaningful consequences (positive and negative). They have ownership and accountability for success. Proactive sponsorship through consistent expectation setting, regular communication, advocacy, and prompting for results pushed the program forward. KM had – and still has – a passionate executive sponsor. In addition, there were individual sponsors for each capability and sustaining sponsorship at varying levels in the organization.
c. All four elements of the construct of **People, Process, Content, and Technology (PPCT)** had to be addressed in a balanced manner. Often technology is the first element a team focuses on when thinking about knowledge management. As an example, this results in force fitting a process around a tool and potentially losing the ability for that process to meet the needs of the audience.
d. **Stewardship, Stewardship, Stewardship** – stewardship roles are critical to provide energy and help people connect. They need to be carefully specified in partnership with internal customers so they are understood and staffed with the right individuals. Each of the above capabilities features a stewardship role central to its success and sustainability. Stewardship roles are great development opportunities for future leaders in the organization, as they become knowledge brokers who understand how to connect people to people and people to knowledge.
e. **Embedding managing knowledge "in the flow"** of business processes is a key accelerator to making knowledge a recognized and valued element of how work gets done.
f. **Tell the story** – the value KM provides is difficult to measure and often confounded with other activities and initiatives. Measurements need to be a blend of qualitative and quantitative ones that can be tied directly back to overall organizational strategic goals and tangible business value. One of the most impactful tactics used was through telling success stories. Success stories helped people understand success though examples from their peers and created personal relevance for them.

The Road Ahead

As the overarching intent of the KM Program in GSTC is in support of the core business objectives of GSTC and Merck, the near term priorities will focus on full realization of the core capabilities discussed. This includes: a) continued expansion to additional users, b) replication of standard KM capabilities to similar knowledge flow problems, c) capability evolution and optimization via enhanced features, and d) ongoing change management and communications. Metrics and corresponding business value will be assessed on an ongoing basis.

In addition, the following further defines the GSTC KM Program for the next two to three years:

- Continue efforts to fully operationalize – that is, to put in the flow – core capabilities
- "Knowledge knows no boundaries," and as such, focus will include expanding to partner groups across Merck
- Opportunistically develop new capabilities to support problem solving and innovation
- Further expand the linkage with creating a high performing organization, including integration with learning and development processes such as new employee on-boarding
- Evolve the linkages between the capabilities to create an integrated "knowledge ecosystem" for knowledge workers to more easily navigate and leverage these capabilities
- Evolve the KM Program Office from strategic initiative leadership to a Center of Excellence on managing knowledge, ensuring long term sustainability of KM capabilities, and providing internal consulting

Conclusion

The term "knowledge management" is a broad and ambiguous term that means many different things to many different people. Hopefully, this article has helped give further meaning to the concept by profiling a practical approach to establishing a plan and supporting capabilities to more effectively manage knowledge. This case study for Merck GSTC highlights some key insights that are broadly applicable, regardless of the scope of knowledge in question. The results of the efforts for Merck GSTC have been quite favorable, delivering benefits in many categories, including improved quality, internal efficiencies, cost reductions and cost avoidance, improved employee engagement, and the ability to leverage a diverse, global, interconnected network. Anticipated future benefits include top line business impact as the capabilities scale.

It is important to understand this strategy has been effective for GSTC; however, KM is not one size fits all. Consider what knowledge matters most to your organization's success, regardless of what your organization does, and tailor your tactics to the business priorities, culture, and practices within your organization.

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Diaphragm Valve Development – Challenging Traditional Thinking

by Per-Åke Ohlsson

This article presents the shortcomings of the traditional diaphragm and demonstrates how changes in the new generation diaphragm valve can reduce maintenance costs, minimize the risk of contamination, reduce pressure drop, and provide better flow regulation.

The traditional diaphragm valve has been a true workhorse for controlling flow of different kinds. Back in ancient Rome, a type of diaphragm valve was used to control the flow and temperature of hot baths. In 1928, a mining engineer from South Africa, P. K. Saunders, invented the type of diaphragm valve that is still used in the industry today.[1]

In the beginning, the diaphragm valve was mainly aimed at non-hygienic applications. However, the valve's simplicity, combined with its hygienic and aseptic design, turned it into a widely used valve for hygienic applications.

Since 1928, the diaphragm valve has seen a lot of improvements. These include new material suitable for hygienic applications, new valve configurations like T, tank-outlet and multi-port valves and a wide variety of automation and control units to operate and control the valve. However, the technology and performance are basically the same as the Romans used for their hot bath, for better or worse.

Even though the diaphragm valve that is widely used in the pharmaceutical industry today continues to work well, it has its shortcomings.

Maintenance

The diaphragm may need frequent replacement depending on applications and duties. The BioPhorum Operations Group (BPOG) has estimated that "up to 40% of preventative maintenance tasks originate from diaphragm valve maintenance."[2]

Contamination and Lost Batches

In the pharmaceutical industry, contaminated and lost batches are expensive. The diaphragm valve has high demands on the tightening of the diaphragm toward the valve body. If the four valve body bolts are not cross tightened with the right torque, the diaphragm sealing to the body will not be optimal. If this sealing is not optimal, the risk of crevices and a cracked diaphragm increases. The diaphragm itself also presents a risk for errors. In a diaphragm valve, the diaphragm elastomer is stretched and compressed. This puts very high demands on elastomer quality. BPOG members also have been seeing varying supply quality.[3] Variations in the quality of the diaphragm may increase the risk of cracking, which potentially leads to contamination of the batches.

Today, it is difficult to tell which supplier offers the longest diaphragm lifetime. The industry is looking for a standardized lifetime test;[2] therefore, some bigger end-users have even invested in their own test-skids to investigate diaphragm materials.

Pressure Drop

The traditional diaphragm valve has a pressure drop that is approximately 20 times higher than a full bore valve, e.g., a ball valve., In a pharmaceutical water system distribution loop, water velocity is crucial in securing the correct temperature and to minimize biofilm in the system. With several diaphragm valves in the system, both the pump and installation work (like valves, tubes and fittings) has to be dimensioned accordingly in order to secure the minimum velocity. This significantly adds to the overall system cost and operating cost compared to a valve with a lower pressure drop.

All Around Performance

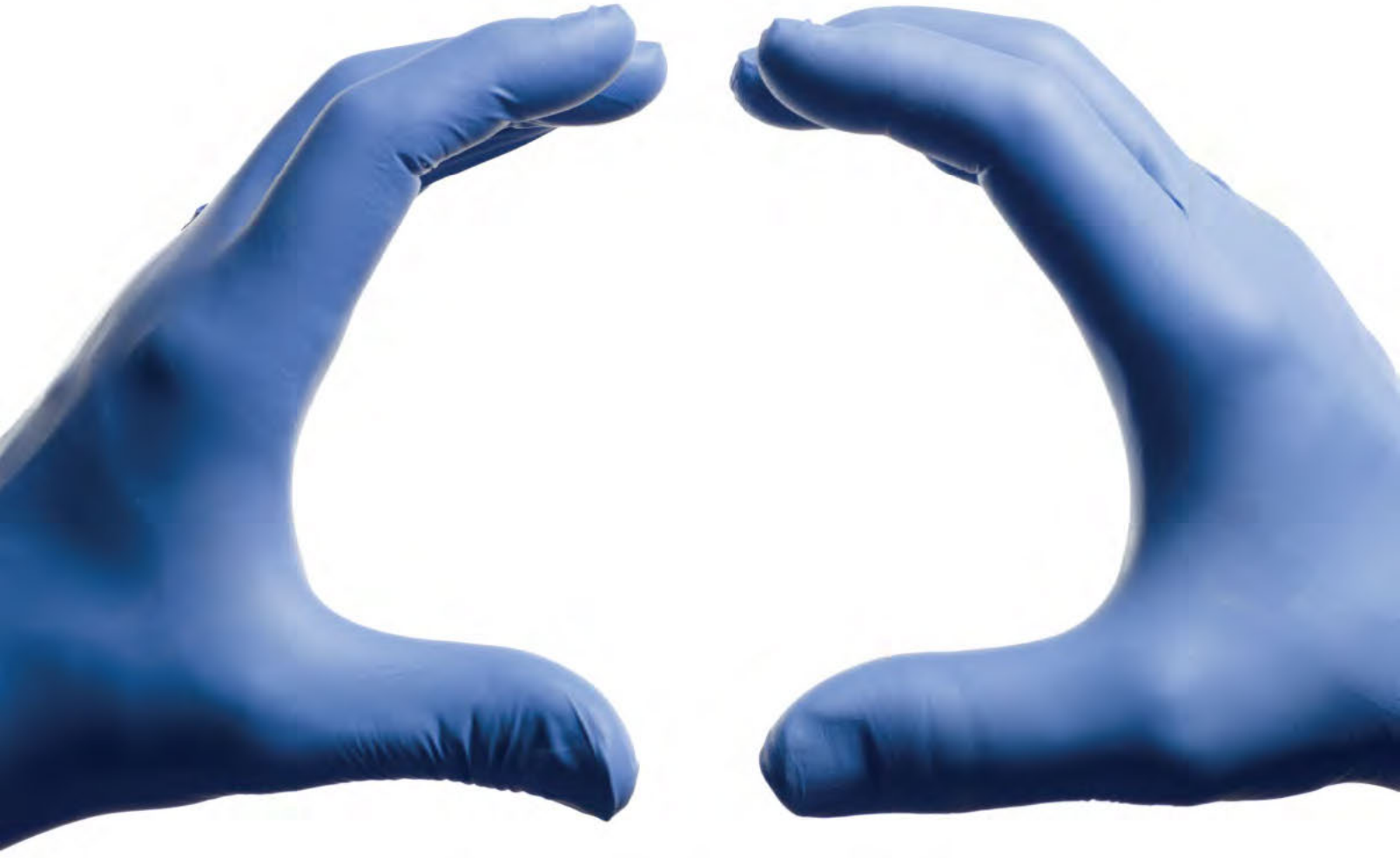

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Figure 1. Comparing the four bolts of the traditional diaphragm value (a) to the centralized thread on the new generation diaphram (b) and the radial diaphragm with clamp assembly (c). The centralized thread provides quick, easy and safe installation as well as service of the valve.

Flow Regulation

The flow curve of the traditional diaphragm valve is only linear up to around 40% stroke opening and thereafter the flow curve drops. This makes it more difficult to control the flow with a diaphragm valve over the entire flow curve of the valve.

Generation Diaphragm Valves

Now some of the largest valve suppliers are developing new diaphragm valve concepts.

These concepts are built around solving many of the shortcomings of the traditional diaphragm valve. They meet the demands in the industry for new innovative solutions providing, e.g., longer lifetime of diaphragms and reducing the carbon footprint with higher efficiency. Innovations vary from small to more radical improvements on the traditional diaphragm valve concept to developments of other valve types like, e.g., radial diaphragm valves.

In these next generation, diaphragm valves there are typically three main changes compared to the traditional diaphragm valve design.

1. New innovative tightening mechanisms for safer and simple assembly - *Figure 1*
2. New diaphragm materials and/or new diaphragm designs such as radial and circular designs - *Figure 2*
3. Design changes improving valve interior - *Figure 3*

Maintenance

Most of the new innovative valve concepts have maintenance improvements. In some cases, diaphragm replacement has been reduced by up to 50%. Typically, there are between 1,000 to 5,000 diaphragm valves in a single pharmaceutical manufacturing site. It takes more than two minutes to service a traditional diaphragm valve. This gives a time savings of 17 to 85 hours every time the diaphragms need replacing.

Another advantage of new diaphragm valve developments are that they do not need retightening after steaming. The traditional diaphragm valve has a larger amount of rubber between the valve body and handle/actuator compared to the new designs. The elasticity of this rubber is affected when the rubber is steam sterilized or exposed to high temperatures; therefore, the valve needs retightening in order to compensate for the reduced elasticity in the rubber material. Most of the new designs also allow for a minimized amount of rubber material between the body and the handle/actuator. The reduced amount of rubber between the body and handle/actuator in the new design minimizes the affect of the elasticity, which means that there is no need to retighten.

Figure 2. Comparing new diaphragm designs (b) and (c) to traditional square diaphragm design (a).

These improvements mean savings both in working and downtime hours.

Advanced Finite Element Method (FEM) analysis has been used to optimize designs, e.g., the new circular diaphragm, will distribute forces and stress more evenly in the diaphragm, compared to the traditional squared diaphragm.

Steam tests[4] have shown that circular diaphragms have approximately twice the lifespan compared to squared diaphragms. This should reduce both the cost for diaphragm spare parts and further reduce maintenance and downtime hours for the industry.

With these new improvements, it should be possible to reduce the high maintenance cost the industry experiences with the traditional diaphragm valve. The future will tell us how great this reduction will be in practice.

Contamination and Lost Batches

Incorrect assembly and tightening of the bonnet over the diaphragm and valve body is one of the main reasons for failure and leakage of the diaphragm valve. If one or more bolts are tightened harder than the other bolts, the forces will be unevenly distributed over the diaphragm. This can lead to leakages between the atmosphere and the product. The uneven forces on the diaphragm also will lead to premature and unforeseen cracking of the diaphragm.

Some of the new designs have a centralized thread or clamp connections that make it very safe and easy to assemble and tighten the bonnet as seen in Figure 1. This secures that tightening is evenly distributed every time. This will minimize the risk of leakage to the atmosphere as well as minimizing the risk for cracking of the diaphragm due to uneven tightening.

The traditional diaphragm valve has often been seen as very easy to clean. However, the sharp corners in the weir and especially in the connection between the body and the diaphragm are areas where flow velocity is very low and which makes these areas rather hard to clean. For really high demands on cleanability, these areas could require extensive cleaning in order to become totally free from residues.

The new developments/constructions of the interior provides a smoother and more corner free design (Figure 3). This ensures that even the highest demands on cleanability will be fulfilled with a quick and simple cleaning procedure.

Figure 3. The new generation diaphragm valve (right) has minimized sharp corners compared to the traditional valve (left) which has sharper corners (circled). The smoother corners reduce turbulence and thereby pressure drop.

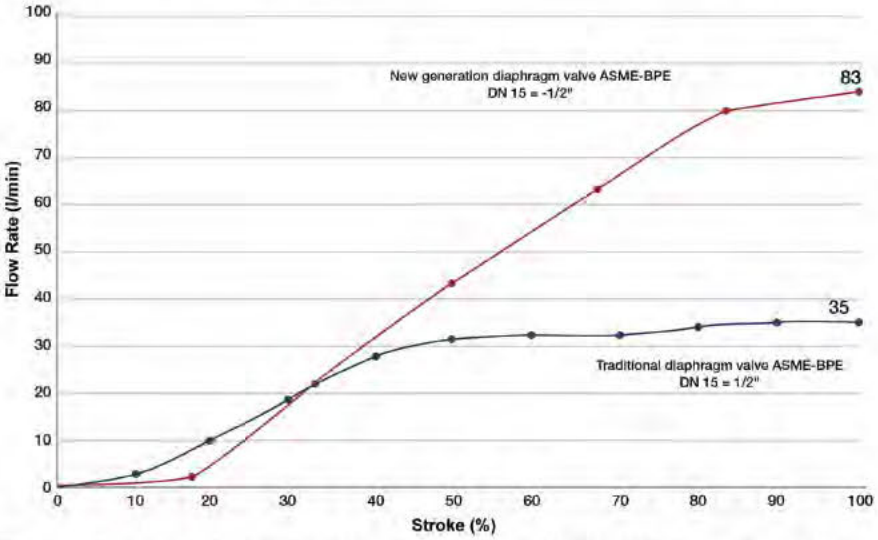

Figure 4. Flow curve of the new generation diaphragm valve compared to the traditional diaphragm valve. The next generation diaphragm valve has a more linear flow characteristic creating a more stable process and better regulating.

Pressure Drop and Flow Regulation

An improved interior design with less sharp corners has two main benefits:

1. It provides a more linear flow curve over a wider area of the valves opening stroke, shown in Figure 4. This now makes it possible to use a diaphragm valve for more exact flow regulation.
2. It improves the flow rate across a range of sizes. The improved flow rate helps to empty tanks faster, reducing system cost and operating cost since the whole installation can be made in smaller dimensions (piping, pumps, etc.)

The small and innovative changes made in the next generation diaphragm valves has really improved the shortcomings of the traditional diaphragm valve and lifted the diaphragm valves to a much higher level in terms of lifetime cost, reliability and performance.

Conclusion

The design of the diaphragm valve has survived the test of time, and has changed little over the last 90 years. Not surprisingly, it has its shortcomings.

By implementing design changes, namely improving valve interior, new innovative tightening mechanisms for safer and simpler assembly, new diaphragm materials and/or new diaphragm designs, radial and circular type instead of a squared type diaphragms, the traditional diaphragm valve performance can be improved.

By challenging traditional thinking the next generation diaphragm valves produce greatly improved efficiencies. It reduces maintenance costs, minimizes the risk of contamination, reduces pressure drop and provides better flow regulation.

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4. All tests and simulations have been performed in Alfa Laval's test facility and laboratory. The steam test has been performed according to The American Society of Mechanical Engineers Bioprocessing Equipment revision 2009 (ASME BPE-2009) appendix J sub-section J-2 Simulated Steam-in-place (SIP).

About the Author

Per Åke Ohlsson is the Global Manager of Pharma and Personal Care at Alfa Laval. He has a MSc in mechanical engineering and a MBA from Warwick University. He is globally responsible for Alfa Laval's fluid handling business into the pharmaceutical and personal care business where he works with strategic business development, product and organizational development. Previously, Ohlsson was with AstraZeneca for five years and held a position as project manager for new drug and device development of devices and medicines for asthma treatment. These projects included the development through pre-studies, clinical tries, pilot scale manufacturing and transferring to full scale manufacturing. Between 2006 and 2008, he also was a member of Pharmaceutical Technology Europe editorial advisory board. Ohlsson also worked for five years as an operations manager in a Swedish battery company, NiMe Hydrid. He can be contacted by email: perake.ohlsson@alfalaval.com.

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Meet Your New Board

The ISPE International Board of Directors 2013 Election has concluded and the results are in. The newly-elected Board will be seated during the Annual Meeting in Washington, DC, USA. Here is the list of those Members who have been elected to serve on the 2013-2014 IBOD.

Officers:

Chair

Damian Greene is Global Network Strategy Lead, Global Manufacturing and Supply, for Zoetis (formerly Pfizer Animal Health) where he is responsible for the company's manufacturing and supply network strategy, product sourcing, and long-range capacity planning. Throughout his 29 year career at Pfizer, he has held leadership roles in Pfizer's Global Supply, Manufacturing, Food Sciences and Chemical Divisions where he has been responsible for API operations, product launch, and network evaluation/restructuring. Greene has been a Member of ISPE for nine years where he has been involved in the API Community of Practice and has chaired the Community of Practice Council. He was elected to the ISPE International Board of Directors in 2007. He holds a BE in chemical engineering from University College Dublin, an MSc in chemical engineering from the University of Missouri-Rolla, and a Certified Diploma in accounting and finance from the Chartered Association of Certified Accountants.

Vice Chair

Andy Skibo is Regional Vice President, Biologics-Supply, MedImmune/AstraZeneca where he affects changes in manufacturing operations, quality oversight, and cross-functional relations throughout the company. Previously, he has worked in other senior leadership roles at Amgen, Genentech, and Foster Wheeler. In these roles, he has been responsible for significant aspects of the companies' operations, including engineering, construction, and validation for large-scale capital projects related to biopharmaceutical manufacturing. He is a member of the International Leadership Forum (ILF), and a member of the Materials Technical Advisory Committee of the US Department of Commerce, specializing in non-proliferation issues associated with biological and chemical weapons. As an ISPE Member for 24 years, Skibo has served on the judging panel for the Facility of the Year Award, he has been a conference leader, and he participates on several committees. He was elected to the ISPE International Board of Directors in 2011. He holds a BS in organic chemistry and an MS in chemical engineering, both from MIT.

Treasurer

Joseph Famulare is Vice President – Global Compliance and External Collaboration at Genentech where he is integral in aligning industry and international regulatory authorities around policy and harmonization, and also heads the company's inspection readiness, GMP auditing and is integral to determining the company's compliance strategies, among other duties. Famulare joined Genentech in 2009 as the Senior Director of Genentech's Quality and Compliance External Collaboration function after a 32 year career at the FDA. He is the former Deputy Director, CDER Office of Compliance, FDA, where he led an extensive team heading GMP GCP, and GLP Compliance programs. He was a founding member and served on the Council of Pharmaceutical Quality. He also held a number of progressive roles at the FDA throughout years of public service. As a Member of ISPE for more than 15 years, he presently serves as a member of the CGMP Executive Planning Committee; Chair of ISPE's PQLI Initiative, serves on the ISPE Regulatory Compliance Committee and is active in ISPE global activities as a speaker and panelist, most recently in ISPE events in Japan and China. He is a member of the International Leadership Forum (ILF). He was elected to the ISPE International Board of Directors in 2010. Famulare has a BS in biology in environmental studies from St. John's University and extensive training in manufacturing, microbiological and chemistry, regulatory risk management and leadership.

Secretary

Mike Arnold is the Business Process Owner for Investigational Products and Senior Director of Strategic Partnerships for Pfizer's Global Clinical Supply Chain. He has worked in the pharmaceutical industry for the past 31 years. Arnold is a member and past-chair of the ISPE Investigational Products Community of Practice, a member of the ISPE Regulatory Subcommittee, a member and past-chair of the ISPE Community of Practice Council, current Chair of the ISPE Strategic Forum, and an active member of the International Leadership Forum (ILF). He is a contributing author to ISPE's Good Practice Guide on Interactive Response Technology and has been a speaker at local and international educational events. In 2011, ISPE

Continues on page 114.

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named him its Member of the Year. Arnold holds a BS in pharmacy from the University of Rhode Island College of Pharmacy and is a licensed, registered and active pharmacist in the state of Connecticut. In 2012, he was elected "Pharmacist of the Year" by the Connecticut Society of Health Systems Pharmacists.

Re-Elected Directors:

James A. Breen Jr., PE, LEED AP is the Vice President, Worldwide Engineering and Technical Operations in Johnson & Johnson's Supply Chain group based in New Brunswick, New Jersey. He has been employed by Johnson & Johnson for 15 years. Prior to this, he worked for the General Electric Company and for Hercules Incorporated on both domestic and international assignments. Breen is past president of the ISPE New Jersey Chapter, a member of the ISPE Facility of the Year Award judging panel, and a member of the International Leadership Forum. He holds a Bachelor of Engineering from Stevens Institute of Technology, an MBA from Drexel University and a Masters of Engineering in Technology Management from the University of Pennsylvania Wharton School. He is a registered Professional Engineer and LEED AP.

Tim Howard, CPIP, PE is the Vice President of Global Operations and Company Officer at Commissioning Agents, Inc. In this role, he oversees human resources development, the company safety program and operations execution. He also provides consulting services for risk management, risk-based commissioning and qualification projects and quality systems implementation. Prior to his work with Commissioning Agents, Howard was a naval nuclear submarine officer, and later became a senior reactor operator at a commercial nuclear power plant. He has been an ISPE Member for 20 years. He presently serves on the Annual Meeting Planning Committee and chairs the Award Committee for ISPE. In the past, he has served as chair of the Carolina-South Atlantic Chapter (CaSA) membership committee and as a CaSA Chapter Board Member. He is a longtime member of ISPE's North American Education Committee, having served as chair and co-chair for three years and as a member of the committee since 2002. Howard earned a BS in mechanical engineering from North Carolina State University. He is a registered professional engineer and a Certified Pharmaceutical Industry Professional (CPIP).

New Directors:

Mark Fitch is currently Senior Vice President of Global Operations for Impax Laboratories, Inc., with responsibilities for manufacturing operations in California, Pennsylvania and Taiwan. He has held positions of increasing responsibility at the Upjohn Company, Schering-Plough, Knoll/BASF Pharmaceuticals, Mylan Pharmaceuticals and Nycomed US, Inc. Fitch has been an ISPE Member for 16 years. He authored a Pharmaceutical Management Training Module for a CPIP course and is a former member of the Editorial Board of the *Journal of Pharmaceutical Innovation*. Fitch is a past Chairman of the PMA (PhRMA) Committee on cGMP and serves as a member of the Dean's Advisory Council, University of Georgia, College of Pharmacy. He holds a BS in pharmacy and pharmaceutical sciences from Purdue University, where he had been recognized as a Distinguished Alumnus. He also holds an Advanced Management Certificate from Northeastern University.

Thomas Hartman is Vice President of GMP Operations, Biopharm CMC, for GlaxoSmithKline, where he leads GMP manufacturing, testing and support operations, and engineering for Clinical Trial Material (CTM) production of biopharmaceutical assets within the CMC group of the Biopharm R&D division. Prior to his 12 year tenure with GSK, he worked for Lyondell Chemical Company (previously ARCO Chemical Company) for 22 years in various engineering and operational roles within the US and Europe. Hartman has been a Member of ISPE for 12 years. He serves as an industry advisor to the Delaware Valley Chapter, participates in the Chapter's annual Owners Advisory Forum and hosts Chapter educational events on the GSK campus. He is active in an industry liaison and mentor role for the Mechanical Engineering Department at Villanova University. Hartman earned a BME from Villanova University and an MBA from Eastern University.

Robert "Bob" Matje, PE, CPIP, is the Senior Director of Engineering at Endo, a position which he has held since June 2012. At Endo, he runs engineering operations for Qualitest, Endo's Generic Manufacturing division, including reliability and maintenance, environmental, health and safety, automation, capital and qualification. Matje worked at Pfizer (then

Meet Your New Board

Continued.

Wyeth) between 1999 and 2012. He held numerous positions, including program manager for Pfizer's Global Serialization Project Management Office and program director for PNS Projects in Puerto Rico. He has been a Member of ISPE for 12 years and is past president of the Delaware Valley Chapter. He serves on the PCC Recertification and Credential Viability Committees, the Facility of the Year Committee, the Community of Practice Council and chairs the Oral Solid Dosage CoP Steering Committee. Matje earned a BS in engineering at Lafayette College and an MS in engineering at Villanova University. He is a Registered Professional Engineer in Pennsylvania and was awarded his CPIP designation in 2012.

Christopher "Chris" Reid is the CEO and Principal Consultant and owner of Integrity Solutions Ltd., a firm that supplies IT project delivery and quality and compliance services in the pharmaceutical, medical device, biotech and healthcare related industries. Reid is responsible for global operations covering ISL's offices in the UK, USA and Japan. Prior to this, he worked for Eutech Limited and Imperial Chemicals Industries plc. He has been a Member of ISPE for 13 years. He is the current Chair of GAMP Europe, the Co-Chair of the COP Council, a Member of the GAMP Council and a Corresponding Member of the Content Evaluation Team. He is also a Steering Committee Member of GAMP UK. Reid holds a BSc (Hons) in computing science from Staffordshire University.

Fran Zipp (Sakers) is the Group Executive Vice President and Head of Quality Operations at Teva, where she reports directly to the CEO. She is responsible for quality and compliance GxP functions globally, as well as QA oversight of IT systems,

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Regulatory Affairs and third-party suppliers. Prior to her five years at Teva, Zipp (Sakers) was employed by Wyeth Pharmaceuticals at the executive level. She also worked at Applied Analytical Industries, Inc. and Novartis. She serves on the ISPE Drug Shortage Working Group and the ISPE Quality Metrics Initiative Team. In addition, she is a member of the International Leadership Forum (ILF), currently serving on Executive Committee. Zipp (Sakers) holds a BS in chemistry from Duke University. She has also done graduate work in pharmacology at the State University of New York at Buffalo and in Management Science at Stevens Institute of Technology.

Directors elected in 2012 serving the second year of a two-year term:

Jennifer Lauria Clark, CPIP, is a Technical Services Project Manager for Commissioning Agents; she is currently providing services to Novo Nordisk on the company's behalf. At Commissioning Agents, she is responsible for business development; project engineering, commissioning and qualification planning, protocol development and execution, project startup and coordination, among other duties. Previously, she held positions at Yonkers Industries where she provided services for Merck, BD, GSK and Biogen and others. Lauria Clark has been a Member of ISPE for 10 years and is actively involved in the Society's local and international activities. She presently serves as the Past President of the ISPE CaSA Chapter, is a member and past chair of ISPE's Young Professionals Committee, and a member of ISPE's Pharmaceutical Engineering Committee and the Annual Meeting Planning Committee. She was also an active student member of ISPE and held progressive roles in her student chapter's board. She has a degree in industrial engineering from North Carolina State University. Lauria Clark earned her CPIP designation in 2012.

Jim Durkin is currently a Project Manager with the National Health Service in the UK, where he is responsible for a new green-field manufacturing facility for sterile products. His prior experience includes similar green-field, start-up projects with Advanced Medical Solutions, Fresenius-Kabi and Astra-Zeneca. Durkin was managing director for Pharmaplan Ltd and was responsiblefor establishing their UK offices. Durkin has been a Member of ISPE for 22 years, a Member of the ISPE UK Affiliate and has been active in many international organizations. He is a Chartered Engineer, Institution of Engineering and Technology and earned a BSc (Honors) in manufacturing engineering from University of Birmingham and Masters in Business Administration from London and Liverpool Business Schools.

Gordon Leichter is the Eastern Regional Sales Manager for Belimed where he is responsible for the positioning and marketing of custom engineered sterilization and washing equipment in the US market. Previously, he held positions with Phar-

ISPE Guide: Cleaning Process Development and Validation

Cleaning Validation is recognized as a key activity to establish that product cross contamination is controlled, helping to ensure patient safety and product quality. It is also an activity which can consume considerable time and resources.

The *ISPE Guide: Cleaning Process Development and Validation* describes a science and risk-based approach for the prevention of cross contamination that, on a case-by-case basis, can determine the scope and degree of cleaning verification.

This Guide is intended to apply to the development and verification of cleaning processes for manufacturing equipment for active pharmaceutical ingredients, dosage forms, biologics, and clinical supplies.

This document addresses how established and accepted risk assessment methods can be used to develop health-based limits, such as acceptable daily exposure and maximum safe carry over values.

An industry review has been completed and the Guide is in the process of being updated to reflect comments received. The Guide is anticipated for publication summer of 2014.

Meet Your New Board

Continued.

madule, Getinge, and Steris among others where he has worked on the operational side of manufacturing pharmaceutical process equipment in addition to sales and marketing roles. Leichter has been a Member of ISPE for 15 years. He has served as board member and president of the New Jersey Chapter, chair of the Sterile Products Processing Community of Practice, co-chair of the Body of Knowledge Committee, as a member of the Supplier Advisory Council, and as a course leader at educational events. He was elected to the ISPE International Board of Directors in 2010. He holds a BSBA in general management and an MS in management from Thomas Edison State College, and a PhD in business administration from Touro University.

Past Chair:

Charlotte Enghave Fruergaard is Partner, Global Consulting for NNE Pharmaplan Denmark where she has 18 years of experience with projects focused on pharmaceutical production, isolator and barrier technology and sterilization techniques. She has led or participated in projects throughout the Nordic region, the European continent, in the US and in Brazil. A member of ISPE for 17 years, she is a founding member of the Nordic Affiliate and served on the Affiliate Board of Directors in a variety of roles including chair. She has been an ISPE conference leader and has participated on the Sterile Products Processing Community of Practice Steering Committee. She was elected to the ISPE International Board of Directors in 2007 and is currently the Vice Chair. Enghave Fruergaard holds an M.Sc. and a PhD in mechanical engineering from Danmarks Tekniske Universitet as well as an EBA in engineering business administration from Copenhagen University College of Engineering.

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For a list of topics to be presented, please visit our website at http://www.ispe.org/2014asepticconference.

Pharma EXPO 2014

ISPE, in alliance with PMMI, the Association for Packaging and Processing Technologies, is gearing up to debut Pharma EXPO, a premiere tradeshow, co-located with PACK EXPO, the world's largest manufacturing and packaging event. Set to take place November 2 to 5, 2014 at Chicago's McCormick Place, Pharma EXPO will feature the total pharmaceutical lifecycle. This new initiative will offer attendees exposure to the latest technologies, the opportunity to attend a full range of education sessions, and a unique opportunity to be inspired by ideas and technologies developed for other industries, reinforcing one of ISPE's core goals to prepare their members to lead global change and innovation in pharmaceutical manufacturing sciences and technology.

In the past, PACK EXPO has brought together 46,000 packaging and processing individuals, more than 2,000 exhibitors, and visitors from more than 130 countries. By aligning with ISPE for Pharma EXPO, PMMI is hoping to attract an additional 10,000 visitors to the event from pharmaceutical, medical device and nutraceutical manufacturers. ISPE and PMMI share a commitment to advance their respective and related manufacturing industries and share the common goal to be leading technical and global resources (ISPE in pharmaceuticals and PMMI in packaging and supply chain). Keeping stride with PMMI's vision of leading technical and global resources, Pharma EXPO will provide a separate, but spacious venue for new and emerging technology, processing and packaging equipment, and other presentations offering advancements in pharmaceutical manufacturing. ISPE is working closely with PMMI to provide new opportunities and platforms for EXPO exhibitors. Impressive locations at this joint-event will provide companies ample occasions for meeting new buyers and building new business relationships. Last year, PACK EXPO's pharma pavilion drew 5,700 visitors alone. In preparation, for Pharma EXPO's inauguration, ISPE and PMMI have planned for more than 1.1 million net square feet of exhibit space.

Along with the vast tradeshow designed to meet the needs of manufacturers and suppliers, ISPE is planning a world class conference program offered during the event. Attendees will have the opportunity to witness cutting-edge technology and attend conference programs that address common challenges in the pharmaceutical life cycle.

With the addition of Pharma EXPO, PACK EXPO is targeted to be the premier North American industry event. Together, ISPE and PMMI, will produce the only show in 2014 to exhibit, as well as educate on all phases of pharmaceutical manufacturing and its supply chains. Exhibitors can expect new opportunities and interactions from big named companies and attendees can expect a complete guide to new technology and the latest in pharmaceutical information.

Stay tuned for more information about how you can participate in Pharma EXPO in future editions of *Pharmaceutical Engineering*.

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Dust Collection Systems and Equipment

Camfil Air Pollution Control, 3505 S. Airport Dr., Jonesboro, AR 72401. (870) 933-8048. See our ad in this issue.

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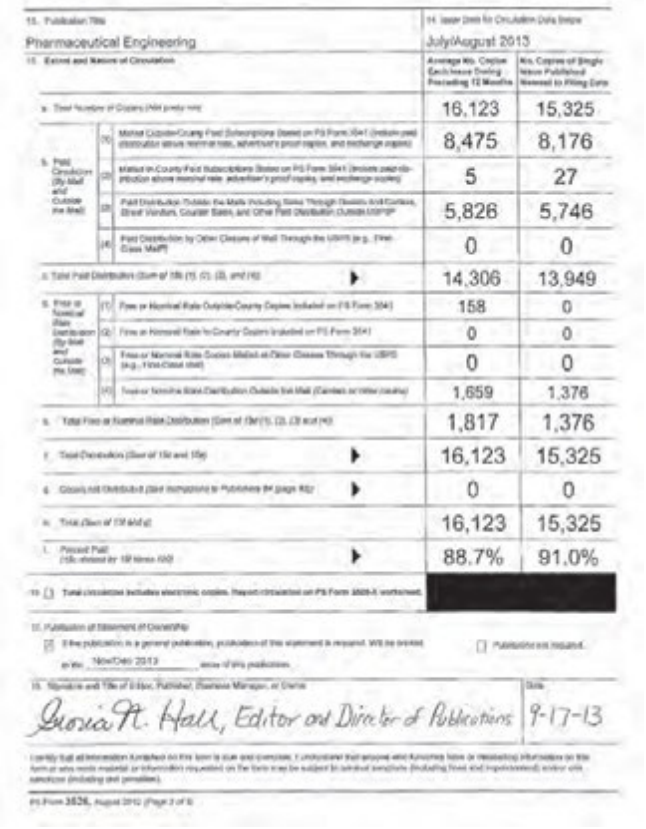

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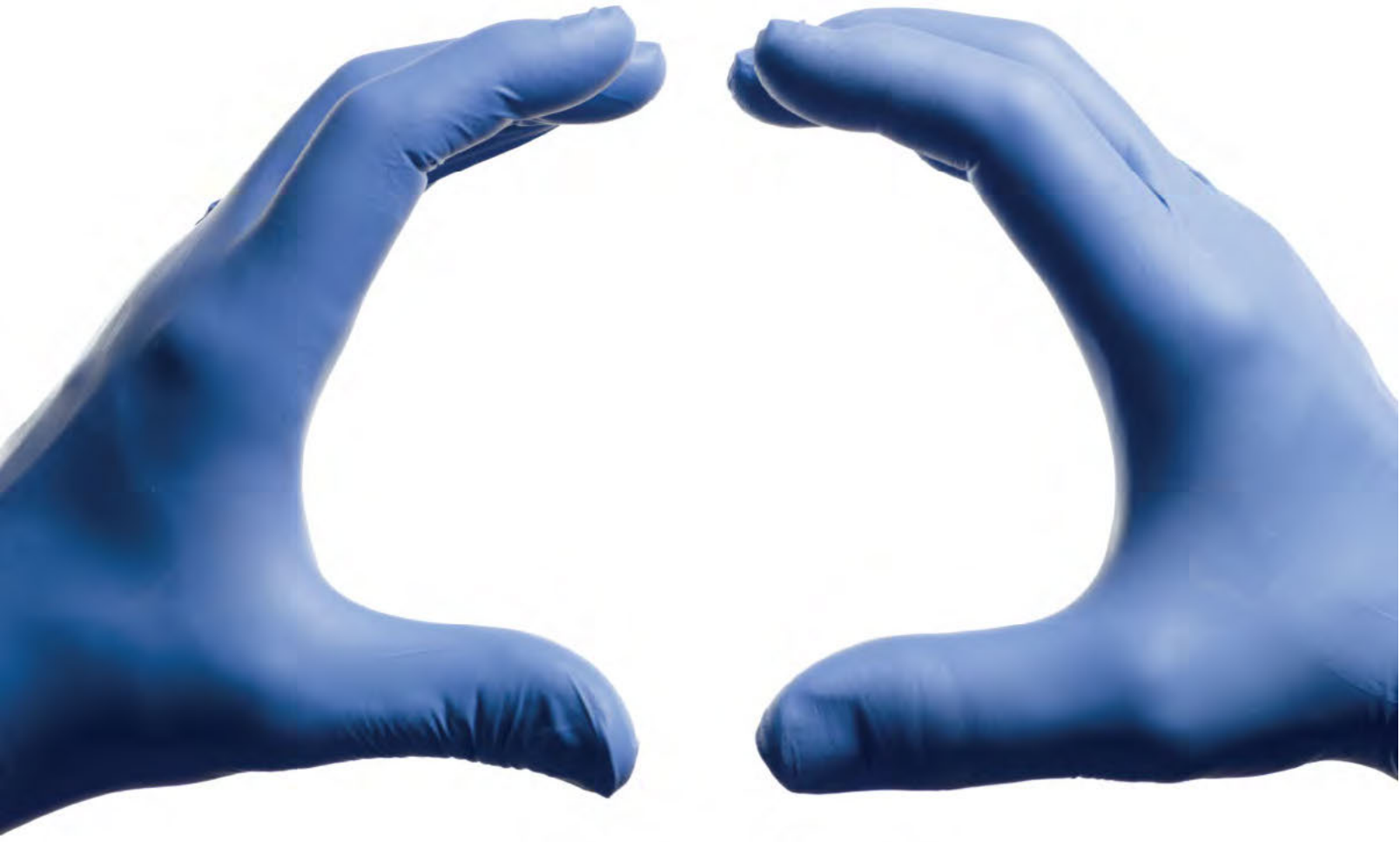

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