This article illustrates the advantages of automated on-line TOC analysis-based water release, discusses critical considerations and possible strategies to employ, and reviews TOC automation in light of the new FDA guidance.

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Automated Release of Water Using On-Line TOC Analysis and FDA Risk-Based cGMP, Inspection, and PAT Principles

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Most pharmaceutical companies in the United States and Europe use laboratory Total Organic Carbon (TOC) analyzers to control the TOC quality attribute for the release of Purified Water (PW) and/or Water for Injection (WFI) for product manufacturing. The goals of this article are to illustrate the advantages of automating this process, discuss critical considerations and possible strategies to employ, and to review TOC automation in light of the FDA guidance documents published in September 2004.

The United States Food and Drug Administration has issued both a final report "Pharmaceutical cGMPs for the 21st Century – A Risk-Based Approach"[1] and a guidance for industry "PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance."[2] These FDA documents encourage the adoption of risk-based approaches to the development of automated process control systems in the pharmaceutical industry. The objectives of these initiatives are lower costs and improved manufacturing efficiency and quality. This risk-based approach is particularly relevant to inspections as explained in "Risk-Based Method for Prioritizing cGMP Inspections of Pharmaceutical Manufacturing Sites – A Pilot Risk Ranking Model,"[3] also published by the FDA.

The automation of drug manufacturing processes in the pharmaceutical industry is not new. However, disruption associated with development of new processes or process improvements that could replace existing validated manufacturing systems is generally avoided in the industry. Previously, there has been little regulatory support for continually changing and improving processes as demonstrated by the many filings required for even the smallest changes. As a result, fixed processes are developed to facilitate easy validation and inspection. The stated goal of these three FDA documents is to facilitate positive change and to encourage the industry to apply a deeper scientific understanding of their manufacturing process by implementing validated critical process controls. When quality is designed into the manufacturing process, well understood and validated process controls produce superior products. Changes in risk-based cGMP inspections also are designed to support these concepts and to encourage continuous manufacturing improvements. In principle, this new approach will provide regulatory relief compared to current FDA inspection methodology.

A rapidly growing number of companies have expressed strong interest in converting to automated on-line TOC analysis-based water release. Many of them have determined that releasing water based on automated TOC analysis may be an effective way to achieve TOC regulatory compliance at a lower cost. Others have expressed an interest in applying automated instrumentation, where possible, to allow a refocusing of the chemical laboratory resources to other critical product quality control and product development areas. Furthermore, the continuous data produced by on-line TOC analyzers can aid in the general management of the water system. It is estimated that as many as 2,500 water loops worldwide are candidates for automated TOC and conductivity compendial release implementation. If the

entire industry were to automate these steps, it is estimated that a net yearly savings of $200 million to $250 million could be achieved.

To develop a better understanding of the state of the industry, companies that have released water using on-line TOC analyzers exclusively, or in combination with laboratory TOC analyzers, were surveyed. From this survey and follow up interviews, both successful and unsuccessful strategies for the use of on-line TOC were discovered. On-line TOC implementation methodologies that best illustrate the major issues, and some of the effective approaches employed to solve them, will be presented.

Pharmacopoeia TOC Compendial Background

TOC analysis was initially specified for pharmaceutical industry use in the first supplement to Japanese Pharmacopoeia (JP) V.12 in 1993, and is currently in effect in the latest JP. The Japanese regulation is applied to WFI produced with membrane processes such as Ultra Filtration (UF) or Reverse Osmosis (RO) and requires that TOC be less than 0.5 mg C/L. The TOC analyzer is to be calibrated at 0.5 mg C/L with Potassium Hydrogen Phthalate (KHP), and the suitability of the TOC analyzer is confirmed by 90% recovery or greater of sodium dodecylbenzene sulphonate (SDBS) at a concentration of 0.5 mg C/L. In November of 1997, the 23rd United States Pharmacopoeia (UPS), Fifth Addendum, Chapter <643> Total Organic Carbon went into effect or promulgated. It replaced the older Oxidizable Substances method for measurement of organics in PW and WFI with the less subjective and more quantifiable TOC analysis. An identical regulation, Chapter 2.2.44, was promulgated in the European Pharmacopoeia (EP) in July of 1999. The USP Chapter <643> is applied to PW and WFI while the EP TOC regulation is required for WFI and is optional for PW.

The current USP Chapter <643>[4] and EP Method <2.2.44>[5] TOC regulations require that the analyzer be calibrated, the suitability of the analyzer for the measurement be periodically demonstrated, and the analyzer have a limit of detection of 0.05 mg C/liter or lower. The test methods can be performed using an on-line analyzer or an off-line laboratory analyzer. The acceptability of on-line TOC instrumentation for TOC attribute testing is dependent on its location(s) in the water system. Additionally, the instrument responses at these

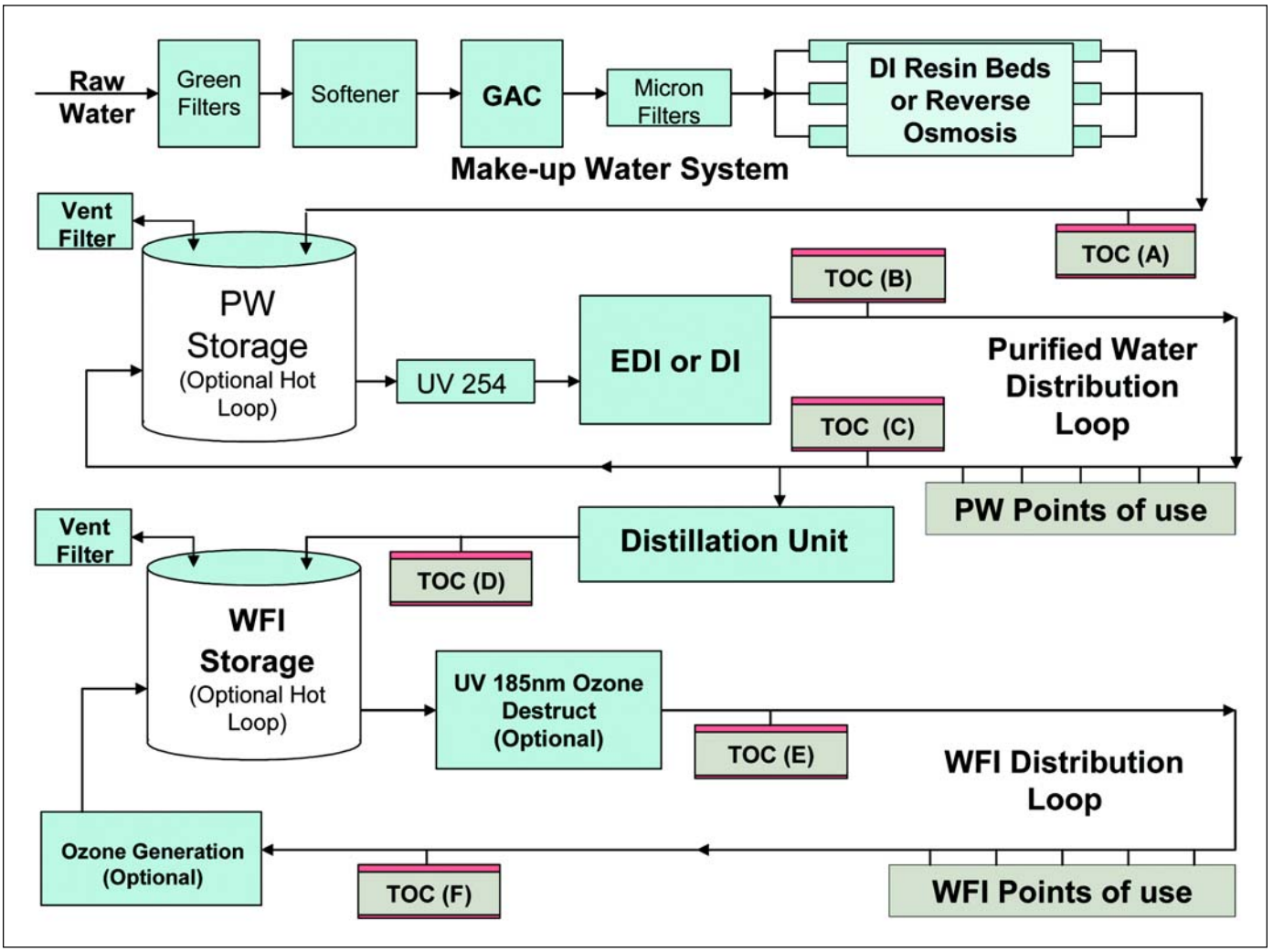

Figure 1. Typical new pharmaceutical water system design (maximum TOC sample points).

locations must reflect the quality of the water used at the point-of-use.

The suitability of the TOC analyzer is determined by testing three solutions, a blank (Rw), a 0.5 mg C/L sucrose (Rs), and 0.5 mg C/L of 1, 4-benzoquinone (Rss). The response efficiency is equal to the result of the calculation:

Response efficiency = 100[(Rss-Rw)/(Rs-Rw)]

The analyzer is considered suitable if the response efficiency result is not less than 85% and not more than 115%. If the analyzer is determined to be suitable and the water being tested (Ru) or the Test Solution is not more than the limit response (Rs-Rw), then the water meets the regulation requirements and can be used to pass the TOC attribute test. This "passed water" can then be released to manufacturing for use in the pharmaceutical manufacturing process.

The System Suitability Test (SST) is a quality assurance measure that demonstrates acceptable TOC analyzer performance for meeting the USP and EP compendial requirements. If the suitability of the analyzer is demonstrated to be acceptable both before and after water testing, the water test results are recognized as acceptable. In the case where the initial suitability test is acceptable, the water can be released to manufacturing, but a second subsequent suitability test fails then *all* the water tested *after* the initial good suitability determination could be suspect. This type of unexpected problem will trigger a costly internal investigation. Proper design of automated on-line TOC release systems can minimize this type of risk. The same risk exists for laboratory TOC based water release systems if the laboratory analyzer has its periodic SSTs done too infrequently.

The USP and EP specifications do not explain the meaning of periodic System Suitability (SS) Testing. The SS testing frequency is determined by the user and is related to value of the water used between SS testing, the costs of the SS testing, the reliability of the analyzer to pass the test, and an internal risk assessment on the product produced.

The FDA and Process Analytical Technology (PAT) Background

The FDA PAT Web page[6] and presentations therein summarize PAT principles. The goal of PAT is to understand 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 next three paragraphs are direct quotes from the Web page introduction section.

"Process Analytical Technology is a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality. It is important to note that the term *analytical* in PAT is viewed broadly to include chemical, physical, microbiological, mathematical, and risk analysis conducted in an integrated manner."

"There are many current and new tools available that enable scientific, risk-managed pharmaceutical development, manufacture, and quality assurance. These tools, when used within a system can provide effective and efficient means for acquiring information to facilitate process understanding, develop risk-mitigation strategies, achieve continuous improvement, and share information and knowledge. In the PAT framework, these tools can be categorized as multivariate tools for design, data acquisition and analysis; process analyzers; process control tools; and continuous improvement and knowledge management tools. An appropriate combination of some, or all, of these tools may be applicable to a single-unit operation, or to an entire manufacturing process and its quality assurance." To be considered a PAT system it must include two or more of these PAT tools.

"A desired goal of the PAT framework is to design and develop processes that can consistently ensure a predefined quality at the end of the manufacturing process. Such procedures would be consistent with the basic tenet of quality by design and could reduce risks to quality and regulatory concerns while improving efficiency. Gains in quality, safety, and/or efficiency will vary depending on the product. These gains can come from reduced production cycle times by using on-, in-, and/or at-line measurements and controls, preventing rejects, scrap, and re-processing, considering the possibility of real time release, increasing automation to improve operator safety and reduce human error, facilitation of continuous processing to improve efficiency and manage variability, and by improving energy and material use and increasing capacity."

This initiative is the governmental basis for cost effective quality improvements, both within the FDA and the industry. The FDA is actively involving its stakeholders in this initiative. The PAT has received support from the "FDA Science Board"[7] and the "Advisory Committee for Pharmaceutical Science."[8] Additionally, the final guidance document

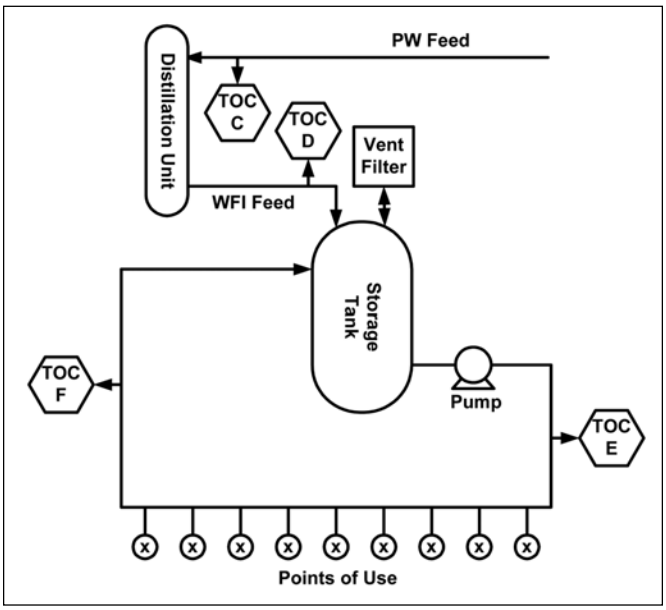

Figure 2. Distillation feed to WFI distribution loop with maximum TOC points.

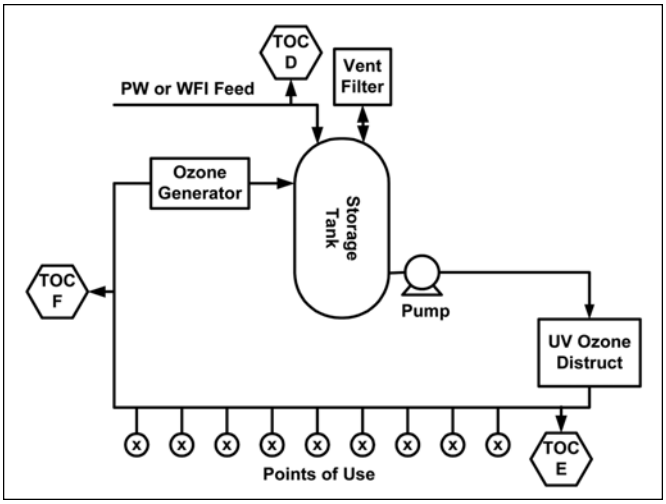

Figure 3. Ozonated distribution loop with maximum TOC points.

was co-authored by the Office of Regulatory Affairs (ORA). This Agency is responsible for enforcement of the FDA regulations. The final report on Pharmaceutical cGMPs for the 21st Century – A Risk-Based Approach" refers to the development of the PAT initiative as a key component for the new FDA philosophy.

Summary of On-line TOC Users Pharmaceutical Survey

In early 2004, a substantial and detailed survey of the users was conducted of on-line TOC analyzers in the pharmaceutical, biotechnology, and biopharmaceutical industries. The survey results demonstrated the importance, expectations, and issues relating to on-line TOC implementation today and in the future. A summary of these results follow.

The respondents were asked to rate the present and future value of using on-line TOC analyzers for four applications: QC release of water to manufacturing, process control, process monitoring, and clean in place. The value of using on-line TOC in each of these categories is expected to increase with time. The release of water to manufacturing was rated the most important, both presently and in the future.

What impact will the FDA have on the use of on-line TOC analyzers over the next five years? The respondents clearly expect that the FDA would encourage on-line use over the next few years. This result may be related to the responders' familiarity with recent initiatives by the FDA to establish improved pharmaceutical manufacturing operations.

How familiar were the respondents with laboratory and on-line TOC analyzers? The typical pharmaceutical user is much more familiar with laboratory TOC analyzers than on-line TOC analyzers. When the implementation of TOC regulations began, it was more common to select a laboratory TOC instrument than an on-line TOC analyzer. Laboratory instruments were considered more useful for evaluating, researching, and implementing TOC for the first time. Because most companies were already required to determine bacteria and endotoxins at many water use points, TOC samples could easily be collected and analyzed in the laboratory along with the other parameters. Since initial implementation of the regulations, many companies have concluded that automation of the TOC measurement with on-line analyzers can be more cost effective and eliminate errors associated with manual collection of samples. Early adopters of on-line TOC have developed a wealth of useful information on approaches to implementing on-line TOC analysis with varying degrees of success. This information is particularly valuable to companies converting or planning to convert or augment laboratory TOC measurement with automated on-line TOC water release process.

The respondents were asked to report the critical factors that should be considered when implementing on-line TOC. The key factors included regulatory expectations, reliability, analytical performance, ease of use, and elimination of manual errors. It can be difficult to run calibration and System Suitability standards on some on-line TOC analyzers. Some on-line TOC instruments impose significant additional operating costs as reported in McCurdy's article *Implementing TOC Testing for USP 23- A Case Study*.[9]

According to the survey, more respondents are using laboratory analyzers for quality control approval of the water TOC attribute. Fewer are using a combination of both laboratory and on-line TOC analyzers for the same. A small fraction is using on-line TOC exclusively for water release. A significant number of people are using on-line TOC for water system process control purposes.

We asked how frequently respondents ran or preferred to run the regulatory required System Suitability Test (SST). The frequency of the System Suitability testing was greater for laboratory instruments than for the on-line TOC analyzers. The SST frequency ranged from performing the test with each water sample to conducting SST once per year. The laboratory instruments where the SSTs were run with each water sample are typically equipped with autosamplers. In this case, it is a relatively simple matter to add the SST standards to the autosampler along with the water samples being tested for compliance. This assures the analyzer is suitable for the specific sample being tested and is the most conservative approach for QC release of water to the TOC attribute. For on-line TOC applications, the value of products produced with the released water will influence the chosen time between SST. Long periods between SSTs can create issues in the event of an Out-of-Specification (OOS) result. If a company elected to do the SST at a frequency of once a year and the analyzer failed the test at the end of that year, how would the company ensure that all the water released during the year was acceptable? This example illustrates the seriousness of the problem and the potential for an investigation of an SST OOS to affect the overall on-line TOC water release economics.

Why Choose Automated On-Line vs. Manual Off-Line Laboratory TOC Analysis?

We visited 10 companies that were in the process of converting or had converted from laboratory based TOC QC water release to on-line TOC based QC water release. We asked them "what were their reasons for converting from laboratory

to on-line TOC analyzers." In all cases, the most important reason expressed was to save operating expenses. This single business factor was also the most critical factor required to ensure the effective completion of the conversion process. Other factors reported were internal efforts to implement manufacturing process automation, elimination of sampling errors, and a refocusing of the laboratory away from routine TOC water analysis to product and research based work. Some larger companies were converting from well-established laboratory TOC analysis to on-line TOC analysis for the first time. We have noted that at many of these sites, the equipment was installed and operational, but the final steps required to automatically release the water to production were not implemented. At most of the new sites, it was also noted that success with the initial study would likely evolve to broad company-wide implementation of water release with on-line TOC instrumentation.

Typical Operating Costs of Laboratory TOC and On-Line TOC

As stated previously, there are a number of compelling reasons to select laboratory TOC analysis as the TOC method of choice for meeting the USP and EP regulations. Laboratory analyzers can be a good choice if there are many water loops, and other TOC applications such as cleaning validation. On-line TOC can be an effective choice for repetitive or routine TOC testing requirements, to reduce frequency of human errors, and to lower operating costs. The cost to implement laboratory TOC varies from site to site depending on the number of sample points, frequency of analysis at each point, and the overall operating cost for each TOC analysis. The operating costs for each laboratory TOC analysis are comprised of labor (analysis, preparation of standards, sample collection, vial cleaning, Out of Specification (OOS) actions, and compliance), and all material costs. The cost depends on the relative efficiency of each site, but we found that it typically ranges from $25 to $40 per sample. At one site in the US, which converted to on-line TOC monitoring from laboratory TOC analysis, the total costs were approximated. The water system at the site included loops for both Water For Injection (WFI) and Purified Water (PW). There were 24 points in the system where both TOC and conductivity samples were collected and sent to the lab for analysis. They had 12 "points of use" where samples were collected five times a week (3120 samples/year) and 12 "points of use" where samples were collected two times a week (1248 samples/year). This site calculated the laboratory TOC operating cost/measurement to be $28. The laboratory also measured conductivity at an operating cost of $7 per measurement. The total operating laboratory TOC costs per year were calculated to be $28 x 4368 or about $122,300/year. The total operating costs for laboratory conductivity analysis was $7 x 4368 or about $30,600/year. The combined yearly operating costs to release water, based on laboratory TOC and conductivity measurement, was $152,900/year.

This site chose to install four on-line TOC analyzers for the water system, replacing the laboratory TOC and conductivity measurements. They placed an on-line TOC analyzer on the inlet and outlet of each water loop (PW and WFI). The cost to install the new analyzers was $120,000. The total cost included the Installation Qualification (IQ), Operational Qualification (OQ), and Performance Qualification (PQ) validation of the four new on-line TOC analyzers as well as the capital costs of the analyzers. The yearly operating cost of the new on-line TOCs is $19,200. The on-line TOC yearly operation cost includes all maintenance labor, consumable expenses, record keeping and regulatory QC compliance labor, and calibration and System Suitability testing costs.

The positive net operating cost savings per year after automation of the TOC and conductivity measurements at this site is $133,700/year. The payback period for converting to on-line TOC and conductivity is projected to be less than 11 months.

Other Benefits of On-Line TOC Use

There are additional benefits for selecting on-line TOC water testing compared to laboratory TOC analysis. The survey indicated "elimination of manual errors" as one of the considerations for implementing on-line TOC measurement. Organics are present everywhere in the factory and in the laboratory so it is easy to contaminate the samples during collection from the factory floor and to subsequently contaminate the analysis in the laboratory. Errors can be made when collecting TOC samples if the operator simply touches or breathes on the sampling vial, standards flask, or sampling stream. It is not uncommon to have sampling points sterilized with ethanol to kill bacteria prior to water collection for biological analysis. If only 0.000038 grams of ethanol contaminates the typical 40 ml sample vial, the TOC will exceed the USP and EP effective limit of 500 ppb as carbon, and there will be an out of specification result produced. In the same way, volatile organics in the air in the laboratory can easily affect the analyzed TOC results if they are not isolated from the TOC analysis area.

At the required pharmaceutical levels of TOC sensitivity, simply cleaning the TOC sample vials properly for accurate results is not a trivial matter as organic carbon compounds are ubiquitous in the laboratory. The typical manual laboratory operations of labeling vials, autosampler loading, analyzer operation, and result calculations can produce human errors resulting in OOS results and require new sample collections and re-analysis of the water. Similar logic also can be applied to laboratory water conductivity measurements.

On-line analyzers automatically collect samples directly from the water system, eliminating many of the possible sources of manual error and sample contamination. Sampling is the weakest link of the three major chemical analysis operations; sampling, sample preparation, and measurement.[10] The use of on-line analytical instrumentation greatly improves both sampling and sample preparation reliability and accuracy, and at the same time can create a significant yearly operating cost savings.

Critical TOC Control Points in a Pharmaceutical Water System

Continuous sampling of the water for TOC allows detection of excursions and provides critical information for improvements to the design, maintenance controls, and service requirements of the water purification system. Control of TOC and conductivity in pharmaceutical water systems can be achieved with analyzer inputs to controllers of proportional recycle valves. The interactive process control capability of new water purification systems resonates with the new FDA initiative, Process Analytical Technology (PAT).[11]

The new FDA initiatives (2004 cGMP and PAT) are designed to embrace the implementation of new manufacturing process and control philosophies. They are now risk-based; which suggests that there is lower risk to new processes and controls when quality is designed in up-front. As defined by the FDA, PAT is "a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality."

To assess the critical parameters associated with real-time TOC release, it is critical to understand the possible sources of TOC variability in pharmaceutical PW or WFI water systems. Once the sources of TOC variability are identified, then a risk assessment of each can be undertaken to determine the most critical parameters. Focusing on the critical parameters simplifies the process and highlights the most likely areas for effective design of analyzer placements and control methods. In this case, TOC can be measured directly with commercially available on-line analyzers and they are utilized in this system design. Other parameters also could affect the final level of TOC in the product water, and therefore, it may be wise to include additional sensors to provide improved process predictably.

For example, reference to Figure 1 will help to illustrate how these ideas might be applied. EPA Drinking water standards mandate a maximum level of 4 mg/L of TOC. Higher drinking water TOC values must be reduced before distribution of the water to the consumer or end-user. USP <643> mandates a maximum level of 0.5 mg/L for all types of pharmaceutical waters and source water must comply with EPA standards. In order to produce USP Purified or WFI waters complying with all mandates, all possible TOC contamination sources must be identified and TOC reduction schemes employed. The first water system section to consider possible TOC variations is the "Raw Water" feed. Excursions of TOC in the source water will affect the final TOC, as each of the TOC removal processes will generally remove a percentage of the inlet TOC. Feed water system TOC excursions will be few if the water source is a deep well, but may be considerable if the water source is from a river or lake. If source water TOC excursions are expected, then a system of recycling unused buffer storage water volume can be used. A raw water TOC excursion can be heavily dampened, and at the final point-of-use, may account for only a few parts per billion of change in TOC. In this analysis process, one must continually ask, how important is it? If the "Make-up Water System" section of the water system uses a Reverse Osmosis (RO) process, this unit operation will achieve the single highest percent TOC reduction in the whole water system. The TOC rejection of an RO system is often between 95 and 99+ percent. Because of this high rejection rate, the use of an RO would minimize the need for additional raw water excursion system protections.

Other areas to analyze include the PW and WFI storage tanks. These tanks exchange air with the outside environment through microbial vent filters. Improper placement of the air intake vents could expose the water to atmospheric TOC excursions.

The PW distribution loop consists of a storage tank, a 254 nm UV light sterilizer, and electrodeionization (EDI) or deionization (DI) resin beds. The PW loop can be cold or hot and may have an ozone system for periodic sanitization. EDI or DI processes remove ionic organics, but rarely add organics. If the water loop is heated, there are typically heat exchangers at each point-of-use. If the main loop heat exchanger leaks, the possible resulting TOC increase will be detected if a TOC analyzer is installed in the loop. If a point-of-use heat exchanger develops a leak, then the TOC at that point-of-use may not reflect the TOC of the loop water and the water would fail this TOC compendial requirement. However, it is rare that a point-of-use heat exchanger will develop such a leak.

Purified water is supplied to a distillation unit to produce WFI. TOC could leak into the WFI water if the main distillation unit were to develop a heat exchanger leak depending on the TOC quality of the hot feed steam. The WFI distribution loop is usually a hot water loop (65 to 80°C). Again, if the loop heating is done with steam or hot water, any lack of heat exchanger integrity could lead to a TOC excursion. In some cases, an ozone system is installed for periodic sanitization. The ozone systems can lower the TOC levels significantly in a recirculating system. In an ozonated system of the design shown in Figure 1, one would expect the TOC level measured by TOC (D) to be higher than that measured by TOC (E).

Current Strategies for Implementing On-Line TOC Analyzers

Over the past 10 years, on-line conductivity and TOC process analytical instrumentation have been installed by some companies to accommodate the United States Pharmacopoeia water monographs.[4,12] Useful information can be gained from their experiences. As indicated earlier, because of the economic benefits, many companies are currently automating their water system's TOC and conductivity measurements. Many of the companies we spoke to were just beginning to study the new FDA cGMP philosophies, and were actively in the process of designing systems for automatic water release. We observed many different implementation strategies from both the past and new installations. Both the USP and EP TOC compendias require that on-line TOC analyzers measure TOC representative of the TOC at the point-of-use. This requires confirmation in the process quali-

fication step by measuring the TOC at each point-of-use and comparing it to the on-line TOC measurement result.

Figures 2 and 3 show the possible placement locations of on-line TOC analyzers within both non-ozonated and on ozonated distribution loops. The following discussions show how the logic for determining the critical TOC sampling points in the system could be developed.

The lowest capital expense approach is to install a single on-line TOC analyzer on the exit of the distribution loop in position TOC (F) just before the return to the storage tank. This approach is effective as long as there are very infrequent issues with TOC analyzer system. With this approach, it is common to use the laboratory TOC analyzer as a backup to the on-line TOC system. The laboratory TOC protocols are already in place and the personnel were already trained to collect the grab samples. Having procedures in place for converting from laboratory TOC to on-line TOC and vice versa in advance is recommended. It is not uncommon for the TOC (F) measurement to be periodically checked and backed up with a laboratory grab sample analysis. It also is useful to have laboratory TOC measurements performed multiple times between the normal periodic on-line TOC analyzers' System Suitability tests. One beneficial strategy being employed is to use the same analytical measuring technology in both the lab and on-line TOC instruments to eliminate the potential instrument response variances. In the case that the on-line TOC fails a SST, the laboratory data is useful to establish the water was acceptable at various times and thereby limit the amount of production water that is brought into question.

We know of one important case where using a laboratory TOC as a backup analyzer will not be as helpful as having a backup dual on-line TOC analyzer system. This instance is where an on-line analyzer has failed the SST and is found to be unsuitable. This introduces the question of whether the water released by this on-line analyzer was acceptable. If a back-up on-line TOC analyzer passes the SST, the questionable "released water" would then be shown to be acceptable. The generation of comparable data with a laboratory analyzer would have required frequent sampling without the knowledge of the imminent failure of the on-line unit.

For operations that can justify the capital expense, there are advantages to installing two on-line TOC analyzers on a single distribution loop. If TOC (E) and TOC (F) can be shown to statistically measure the same water, when arranged as shown in Figures 2 and 3, then they are effectively redundant and either one can be used as backup. It is not necessary to install a back-up TOC at the same sample point in the loop. The later arrangement provides the additional information on water loop TOC changes from possible contamination points between the two analyzers. The dual on-line TOC approach is more robust than a single on-line TOC approach, primarily, as any problem with one TOC analyzer does not prevent the continued operation of the automated system. If one TOC analyzer needs service, maintenance, or if the SST fails, the second analyzer can be used as backup and the automated process can continue uninterrupted. The capital expense is higher for this approach; however, it is still common to achieve payback of the investment within one year. Of the two different approaches, the dual on-line analyzer per loop is clearly the least problematic in actual implementation.

The placement of the analyzers TOC (C) and TOC (D) as shown in Figure 2 or Figure 3 is to ensure the WFI or PW purification system is operating correctly. Many sites use an on-line TOC analyzer in one or both of these locations to ensure these processes are under control. It is possible to statistically prove either TOC (C) or TOC (D) analyzer is measuring the same TOC as that of either TOC (E) or TOC (F), but there can be a small risk the distillation unit or distribution loop may add TOC due to a system failure and negate their effective use as backup TOCs. If the risk of TOC intrusion from the water loop or the distillation unit is considered to be low, then the use of the pair of either TOC (C) or TOC (D) and either TOC (E) or TOC (F) analyzers has the advantage of both checking the performance of the feed water systems and providing backup duty. However, this is not possible with the ozonated water loop as shown in Figure 3. The TOC difference between the feed water and the loop is likely to be different. The ozone can oxidize some of the TOC to CO_2 and decrease the TOC level in the loop compared to the TOC in the feed water.

Figure 3 shows a typical ozonated loop system. The most common approach in an ozonated water loop is to place a single TOC analyzer at location TOC (F). Often the WFI or PW supply also will have a TOC (D) analyzer to ensure the water purification system is working properly. The use of redundant analyzers TOC (F) and TOC (E) is the most robust approach for the reasons previously stated.

For the proper implementation of an automated real time TOC release system, the computer, data acquisition, process sensors, process equipment, and process analytical instrumentation should be well integrated into a comprehensive management system. A comprehensive management system ensures the continual operation of the process within proscribed limits ensuring product quality. The GAMP guidance provides valuable help in designing the process control systems.[13] The 21 CFR Part 11 rules will apply for controlling and protecting the integrity of the data so it is important to select equipment that supports 21 CFR Part 11 requirements. The FDA is examining industrial feedback on this rule and is expected to issue new guidance early in 2005. In spite of the various difficulties, progressive companies in the pharmaceutical industry have already been implementing new process controls and control system via Supervisory Control and Data Acquisition Systems (SCADA), Distributed Control Systems (DCS), Facility Monitoring Systems (FMS), Programmable Logic Controllers (PLCs), and Man-Machine Interfaces (MMI). These systems have increased the usage of analytical and on-line sensors in automated processes. The recent PAT guidance documents offers an opportunity to substantiate the operation, control, and monitoring of water systems by integrating automation, sensory data, and feedback mechanisms with the target of implementing PAT and

on-line instrumentation for automatic formal QC water release to production.

Risk-Based Method for Prioritizing TOC Measurement Points

The various possible TOC points should be analyzed from a risk-based perspective to help assess the optimum critical instrument locations. "The need for applying a risk-based ranking process is driven by the disparity between obligations to manage, mitigate, or reduce an array of risks (or many sources of a given type of risk) and available resources."[3] Risk categorization and risk ranking or similar approaches have been described by Haimes,[14] Ayyub,[15] Health and Safety Executive,[16] and Morgan et.al.[17] These sources were referenced in the FDA's "Risk-Based Method for Prioritizing cGMP Inspections of Pharmaceutical Manufacturing Sites – A Pilot Risk Ranking Model."[3] It is expected that pharmaceutical automation processes and control systems should have a risk assessment model developed to justify the final engineering design choices.

PAT Framework and Real-time Compendial Water Release

Water is a common excipient and the most common ingredient used in drug manufacturing and it is always manufactured onsite. There are many advantages to be gained by applying the PAT framework and working with the FDA's PAT team to implement automatic compendial TOC and conductivity release system. The PAT Guidance for Industry[2] describes what elements are needed to qualify a control system to fit within the PAT framework. The section in the guidance on "Principles and Tools" requires a PAT system to have at least two of the four described tools, and there is a subsection describing Real Time Release. Some of the elements that would need to be shown are an understanding of the TOC or conductivity removal/addition processes in the water system, understanding of possible sources of conductivity or TOC, the determination of critical TOC and conductivity control points, implementation of TOC and conductivity analyzer(s), and a control system to satisfy the compendial requirements. A PAT System is not simply replacing a laboratory TOC analysis with an online TOC analysis. There must be a control element involved, whether automatic or manual. The guidance document section on Real Time Release includes the statements, "Typically, the PAT component of *real time release* includes a valid combination of assessed material attributes and process controls." "The combined process measurements and other test data gathered during the manufacturing process can serve as the basis for real time release for the final product and would demonstrate that each batch conforms to established regulatory quality attributes. We consider real time release to be comparable to *alternative analytical procedures* for final product release." "Measurements, controls, and "real time" release based on PAT are expected/likely to be "private" or company standards (alternate analytical procedure)."[18] The FDA requests that prior approval be attained if the product is subject to market applications or licenses. This is not the case for water. Real time release, as described in the guidance, meets the requirements of testing and release for distribution (21 CFR 211.165).

A well understood process implies that "all critical sources of variability are identified and explained. Variability is managed by the process. Product quality attributes can be accurately and reliably predicted."[19] It is recognized that not all process knowledge can be achieved prior to actually operating the process and learning from it. The analysis of the data can be done using many possible statistical and mathematical tools to arrive at a deeper process understanding. One of the tenets of the new FDA concepts and in particular the PAT initiative is continuous process improvement and the associated changes will be embraced by the Agency. This is often interpreted as regulatory relief for process improvement changes. A well understood process can simplify the Agency's validation approach, as risk is inversely proportional to process understanding.

The following quotations are from Dr. Ajaz Hussain, Deputy Director, Office of Pharmaceutical Science, CDER, FDA and Chairman of the FDA PAT Steering Committee as presented on 4 May 2004 at the EDQM Spring Conference in Cannes.[20] "Process understanding can provide a high assurance of quality on every batch and provide alternative, effective mechanisms to achieve validation." He continues with the remark "process validation can be enhanced and possibly consist of continuous quality assurance where a process is continually monitored, evaluated, and adjusted using validated in-process measurements, tests, controls, and process endpoints." He further states "process understanding can justify real-time release." Where "real-time release is the ability to evaluate and ensure acceptable quality of in-process and/or final product based on process analytical data."[21] If the new processes or changes are developed through close communication with the FDA PAT team, some degree of compendial regulatory relief may be possible. And finally, he says "The optimal application of the PAT Framework can assure quality is built into the product and process by design. Therefore, companies utilizing this framework will not have to worry about non-conformance to compendial monographs (since such risks would be mitigated by design and the risk level is expected to be lower than the corresponding current risk level). However, this aspect of PAT is not widely appreciated and some companies seek further clarification on issues with compliance to pharmacopeial monographs for situations with larger sample size for analysis."[21]

One of the goals of the final PAT guidance is to tailor the Agency's usual regulatory scrutiny to meet the needs of PAT-based innovations that (1) improve the scientific basis for establishing regulatory specifications, (2) promote continuous improvement, and (3) improve manufacturing while maintaining or improving the current level of product quality.[22] An automated "real time release of water" system using an on-line TOC may fit within the PAT framework if it includes two or more of the basic PAT tools.[2] If the proposed

process is determined to be a PAT process, the PAT team will provide guidance on the most appropriate implementation approach. The PAT team recommends contact as early as possible to clarify and simplify the PAT implementation.[23] To facilitate adoption or approval of a PAT process, companies may request a preoperational review of a PAT manufacturing facility and process by the PAT Team (see the ORA Field Management Directive No. 135).[24]

The compendial regulation is written in a way that supports the use of automation. The USP and EP TOC regulations suggest the use of on-line TOC as an effective means to achieve compliance as long as the on-line TOC results are representative of the TOC of the water being used and, in principle, are in harmony with a PAT system.[25]

Conclusions

The responses to the pharmaceutical TOC surveys provide insight into on-line TOC analyzer implementation. The most important application of on-line TOC analyzers is to provide the TOC data of record for regulatory QC release of water for manufacturing use. The use of on-line TOC is expected to be encouraged by the FDA in the next few years. This is a result of efforts by the FDA to encourage the improvement and design of automated process systems for manufacturing drugs.

The current approach to TOC analysis is most often accomplished with the use of laboratory analyzers or the combination of laboratory and on-line TOC analyzers. Only a small fraction of the surveyed companies are using on-line TOC today exclusively for release of water. Survey results also suggest a trend toward greater use of on-line TOC over the next several years.

Many companies are currently evaluating or are in the process of converting to on-line TOC from laboratory TOC analysis. A major factor driving this effort is the significant operating cost savings that can be achieved. Payback from a conversion to the robust dual on-line TOC analyzer per distribution loop approach can be a year or less. This payback depends on the cost of the laboratory TOC analysis, the number of "points of use," and the frequency of TOC measurements at each "point-of-use" being analyzed in the laboratory. The cost of sample collection can be high and is often the weakest link in the analytical measurement process. Collection of TOC samples and TOC analysis in the laboratory can be influenced by environmental contamination. On-line TOC analyzers eliminate many sample collection and manually induced errors. For those companies using a combination of lab and on-line TOC analyzers, standardizing on the same analytical instrumentation technology can eliminate analytical variability common with disparate measuring technologies.

The implementation of dual on-line TOC analyzers for each water distribution loop enables a superior level of robustness in the process compared to a single on-line analyzer. The TOC output from the on-line TOC analyzer must be representative of the TOC at the "points of use" in the distribution loop and this relationship must be confirmed in the process qualification of the analyzers during validation.

New FDA philosophies as stated in "Pharmaceutical cGMPs for the 21st Century – A Risk-Based Approach" are highlighting the value of applying knowledge and process understanding to automation of manufacturing processes. Risk analysis is fundamental to critical process understanding. The PAT team formed within the FDA has developed guidance documents for the implementation of automation and control to new and old processes. When the PAT framework is properly applied, product quality will be equal to or better than that produced with prior manufacturing processes. They also will be more economical and new cost effective regulatory approaches can be used.

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This article reviews the major concepts of equipment CIP and issues related to the overall layout of modern biopharmaceutical facilities.

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Equipment Cleaning-In-Place in Modern Biopharmaceutical Facilities: Engineering Concepts and Challenges

by Leonid Shnayder, PhD, PE and Maria Khanina

One of the authors recently had to estimate average daily usage of water and generation of the wastewater in a major biopharmaceutical facility. As expected, equipment Cleaning-In-Place (CIP) was found to be one of the largest contributors to the water loads. However, the actual volumes used for the CIP operations exceeded expectations: the plant is using, on average, more than 2000 gallons of water to clean a piece of process equipment and associated piping. Why so much water? Before answering this question and making recommendations for improving the situation, let us review the major concepts of equipment CIP, as well as some of the issues related to the overall layout of modern biopharmaceutical facilities.

Typical CIP System Design and Operation

Figure 1 shows a schematic diagram for a typical CIP system. It includes a wash tank used for preparation of cleaning solutions and for their recirculation, optional tank for purified water used for the final rinse, CIP supply/recirculation pump, metering pumps for cleaning chemicals, heater, instrumentation and controls.

The CIP Supply (CIPS) line is connected to the spray devices located in the vessel or other piece of equipment that needs to be cleaned. The cleaning solutions exiting such vessel can be routed back to the CIP skid either by gravity (where feasible) or via a low-speed CIP Return (CIPR) pump. Upon return to the skid, the

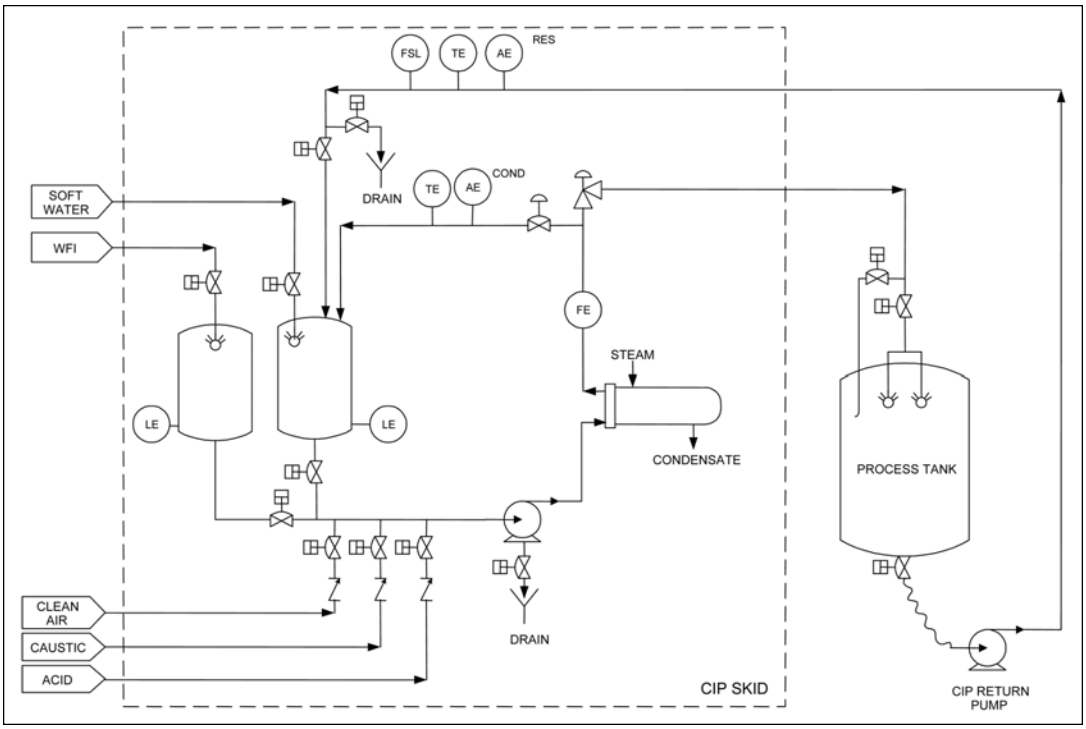

Figure 1. Simplified flow diagram of a typical CIP system.

solution can either be recirculated into the CIP supply line, or diverted to drain.

In order to overcome commonly found difficulties with returning the cleaning solutions back to the CIP skid, it was suggested to use the eductor-assisted CIP return approach.[1,2] The CIP system in that case (Figure 2) includes a motive pump recirculating the cleaning solutions through an eductor, creating vacuum in the CIP return line connected to it. The mushroom-shaped recirculation tank is used for air disengagement from the CIPR stream, and allows keeping positive suction head for both the motive pump and CIP supply pump with minimum amount of solution in the system. The skid also may include hold tanks for softened water and/or purified water; these are needed if the existing distribution system for either grade of water cannot supply the high flow rate required for CIP (typically 30 to 60 gpm, sometimes even higher). The eductor-assisted CIP systems offer improved hydraulic performance and reduced consumption of water and chemicals due to more effective evacuation of the cleaning solutions from equipment and piping between the steps.

Equipment CIP cycle used in a biopharmaceutical facility may consist of the following steps:

- Pre-Rinse
- Caustic wash
- Air blow
- Rinse
- Acid wash
- Air blow
- Rinse
- Final rinse
- Air blow

The caustic and acid wash steps are usually performed with the cleaning solution recirculating in the CIP circuit in order to provide sufficient contact time for the cleaning action with minimum amounts of water and chemicals. For all the rinse steps, the water flow is once through. In some cases, the rinses are performed in the pulsing fashion (supply to the spray devices is on for a few seconds then off for a few seconds, allowing solution to drain from the vessel, then on again etc.). Air blows are used to empty the CIP supply piping between the steps, thus reducing the amount of water needed to rinse the wash solution out of the circuit.

Not all of the above steps are always used; for example, some cleaning recipes do not include a recirculated acid wash. Sometimes an acidified rinse intended to remove the traces of caustic is used instead. In other cases (such as for buffer hold tanks), cleaning is achieved by simply rinsing a vessel with purified water without using any chemical solution at all.

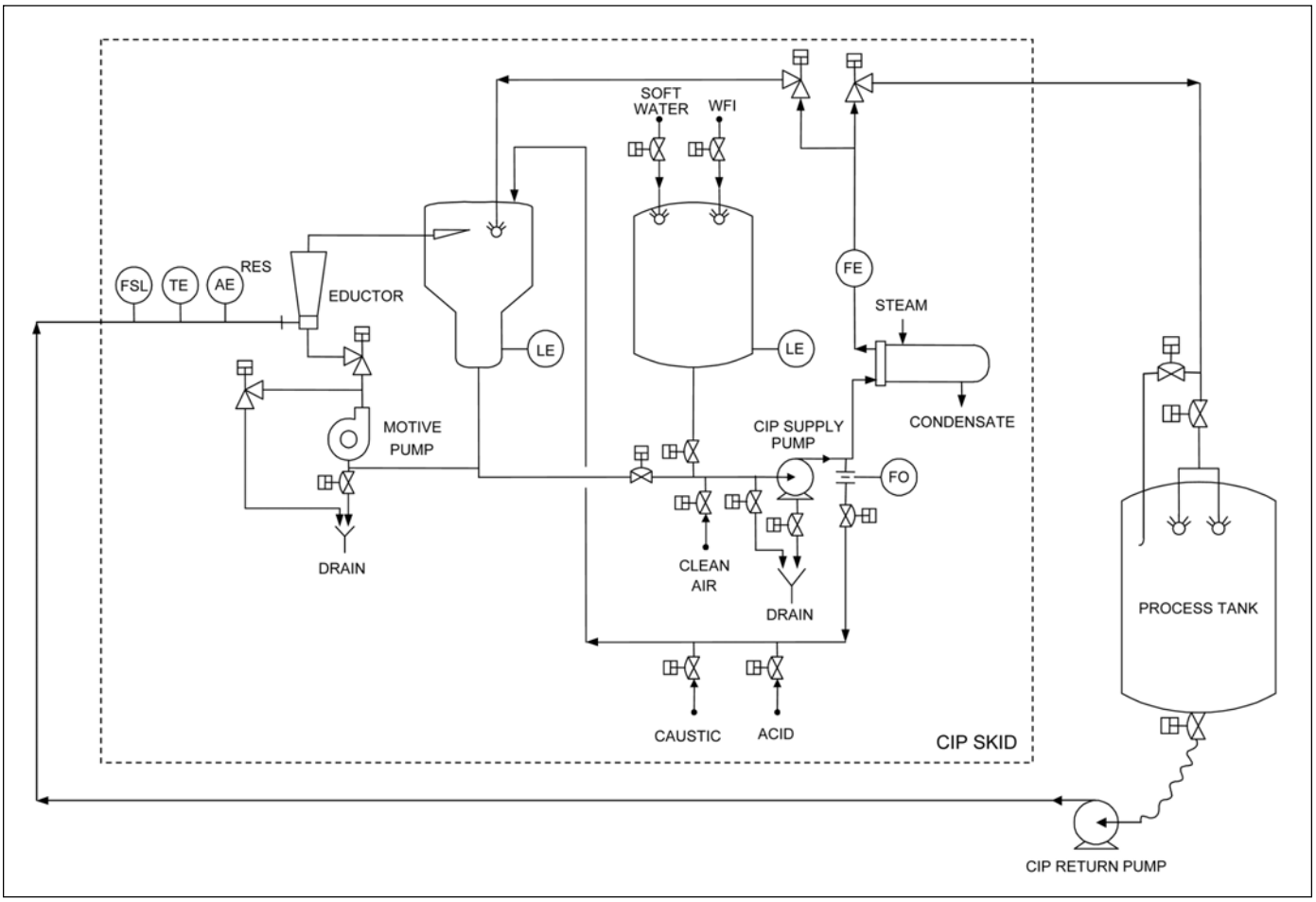

Figure 2. Conceptual flow diagram of eductor-assisted CIP system.

The water used for the final rinse shall be of the same grade as the water used in the corresponding process: in the pharmaceutical industry, that usually means either USP Purified Water or Water-For-Injection (WFI). As for all other rinse and wash steps, the water quality is up to the user. Potable or softened water works fine although many companies choose to use higher grades for various reasons. It is not uncommon to see deionized or USP Purified Water used for all such steps, and WFI for the final rinse. Some biopharmaceutical facilities use WFI for all their cleaning needs.

CIP Distribution Concepts

Initial CIP systems developed for the dairy industry in the 1950s were portable.[3] Such a system (Figure 3) was wheeled next to the piece of equipment being cleaned, connected to the source of water and other utilities as needed (power, steam, drain), and connected to the spray devices and to the equipment outlet with hoses. While portable systems are relatively labor intensive, they have two major benefits: low capital cost (no need to install a lot of CIP supply and return piping, transfer panels etc.) and low usage of water and chemicals (because cleaning circuit is very short).

To avoid the labor and inconvenience associated with moving a portable CIP skid around the plant, and to achieve a higher level of automation, companies started to install fixed CIP systems. A fixed system may look like the schematic shown in Figure 1. Some systems also include one or more additional tanks for recovery of various wash and rinse solutions (this is not common in the pharmaceutical industry), and features like an eductor with a motive pump to facilitate the return of the cleaning solutions to the CIP skid - *Figure 2*. One fixed system can serve 5 to 20 pieces of process equipment depending on the frequency of cleaning required for each piece, and the complexity of the cleaning cycle, which translates into the CIP cycle time. The CIP skid is connected to all the process equipment it serves via elaborate network of supply and return piping. Where feasible, portions of the process transfer lines are utilized to deliver the CIP solutions so that the amount of piping that needs to be installed specifically for CIP is kept to a minimum. The important features of the CIP supply and return piping networks are:

Figure 3. Portable CIP system. (Courtesy of Electrol Specialties Co.)

- The piping needs to be configurable to wash any one of the pieces of equipment, or more accurately, any of the CIP circuits served by the system.
- The piping needs to be designed in such a way that it is thoroughly cleaned with any of the circuits (no "dead legs" etc.).
- The pressure drop and hold-up volumes in the CIPS and CIPR piping shall be kept to reasonable minimums.

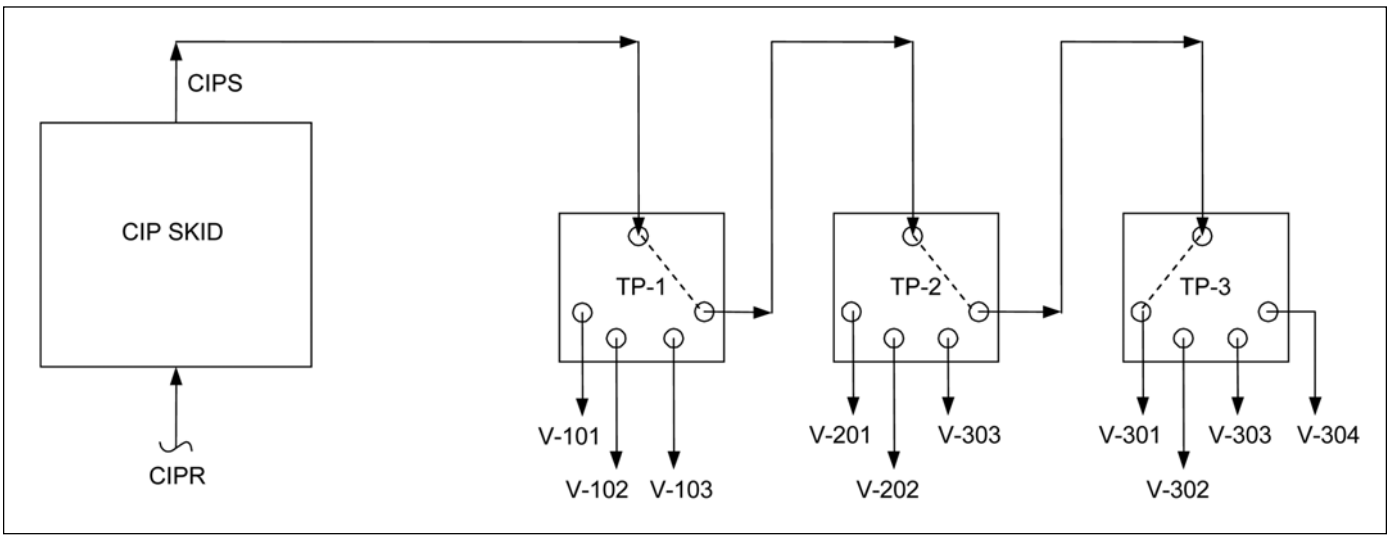

Figure 4. CIP distribution system with multiple transfer panels in series.

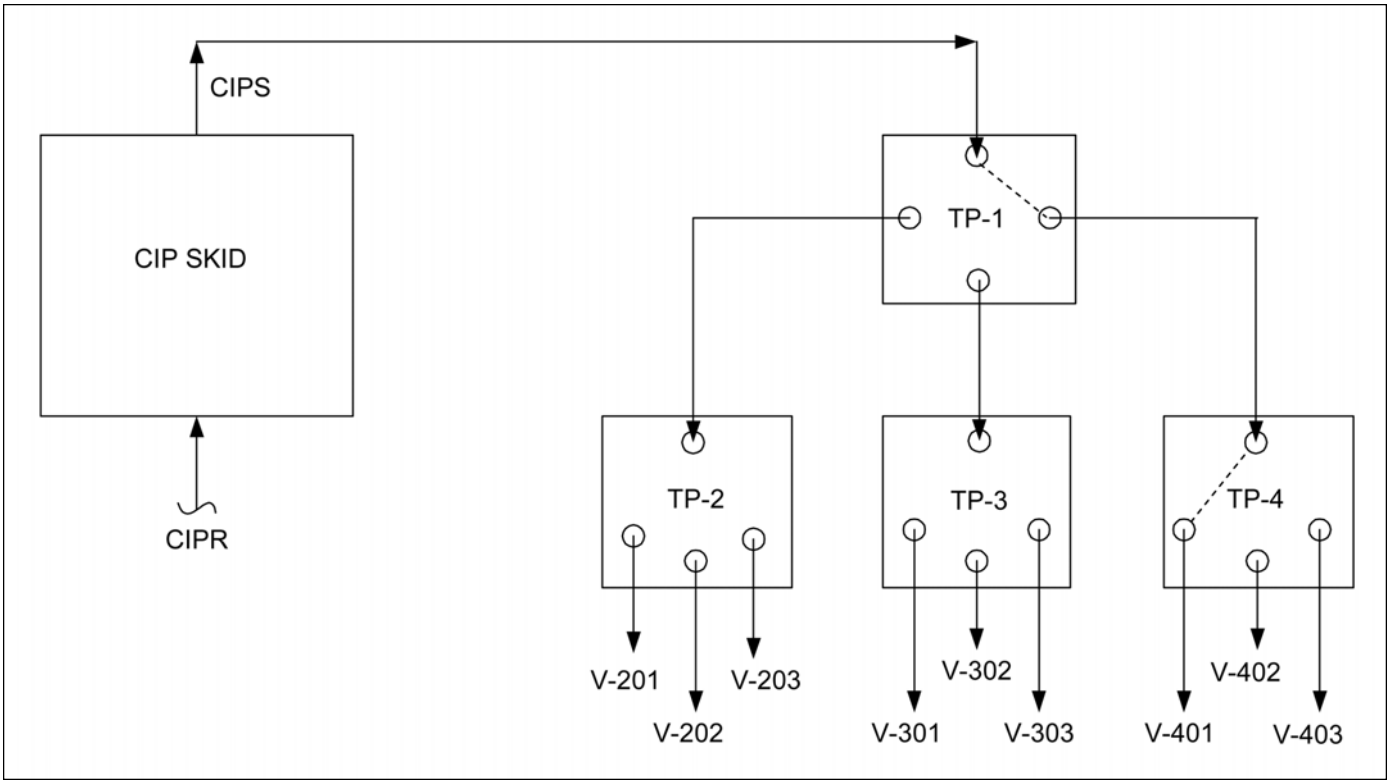

Figure 5. CIP distribution system with master transfer panel.

Some of the possible designs for the CIP distribution networks are shown in Figures 4-7.

Figure 4 illustrates the design with the CIP supply piped to one transfer panel (TP-1), where it can be diverted either to one of the process vessels V-101, V-102, V-103, or to a line leading to the next transfer panel (TP-2), serving the next group of process vessels. This way several local transfer panels can be connected in series. The downside of such design is the high pressure drop and solution hold-up volume in the CIPS lines. To minimize this problem, designers often employ a "master CIP transfer panel" or valve manifold concept (Figure 5 and Figure 6), where a dedicated CIPS line serves each of the local transfer panels. With the valve manifold, the dead legs can be avoided either by providing two valves at each branch point or by installing a drain valve (such as YV-01 on Figure 6) at the end of the CIPS header. In the latter case, one valve per branch is enough, but the drain valve needs to be pulsed open at the end of each of the wash and rinse steps as part of the CIP program. Depending on the equipment layout, the CIP distribution valves may be scattered around the facility (as implied in Figure 6) or they may all be clustered in the vicinity of the CIP skid.

Another alternative is to install the CIPS piping in a loop form (Figure 7), where CIP solution leaving the skid splits into two streams and is delivered to each of the multiple destinations from both sides of the loop, thus avoiding any dead legs. The loop is made out of smaller diameter piping (usually 1.5" as compared to 2" for most CIP distribution systems) since any particular section of it carries roughly half of the flow. To be exact, the flow split between the two loop sections depends on their relative lengths, and therefore varies from one CIP circuit to another. Some people express concerns about that (how do you validate the exact fluid velocity in each section?), but experience shows that properly designed systems of this type work satisfactory.[1]

The CIPR piping also can be arranged in various ways: from simple branched piping system with check valves to more complex arrangements similar to the ones used for CIP supply. Where feasible, the cleaning solutions are returned to the CIP skid by gravity, but more often a portable or fixed CIP return pump is employed.

In large plants, it is common to see multiple CIP systems, each serving a particular process area. One reason for that is a simple issue of equipment utilization: how many cleaning cycles each CIP skid can perform per day. Another reason is the desire to separate services for various process areas. For example, in biopharmaceutical plants, we often find dedicated CIP skids for media prep, cell culture, buffer prep, initial purification, and final purification areas.

Water Usage for CIP

As we mentioned before, fixed CIP systems offer some advantages over portable systems, especially in labor savings and extent of automation. However, they also may have one major disadvantage: the hold-up volume in the CIP supply and return piping. The longer the piping, the more water is needed to wash and rinse the cleaning circuit. The CIP cycle time, amounts of chemicals, and plant steam (heating medium) required also are increased. It has been reported[3] that the amount of water needed to rinse a wash solution out of a pipe section is at least 1.5 to 2 times the internal volume of such pipe. The actual rinse volumes in the pharmaceutical

industry tend to be 4 to 5 pipe volumes due to more stringent acceptance criteria based on the final rinse conductivity.

And, here is where the problem starts. If you ask any CIP expert, he or she will tell you that the CIP skid should be located as close as practical to the process equipment it serves. When the CIP skid is installed within 50 to 80 feet of the process equipment, it is possible to wash an average size tank (say, up to 1,000 gal) with 400 to 500 gal of water or even less. You do not need a lot of cleaning solution to wash a tank. The amount required is determined by the need to keep the CIP supply pump (and CIP return pump, if used) primed, to maintain reliable level control in the wash tank, plus the volume of the CIP supply and return piping. While some well-designed systems can operate with as little as 30-35 gal of water in the circuit,[2] not much can be done about the hold-up volume in the supply and (to a lesser extent) return piping.

However, if you look at the layout of most modern large-scale biopharmaceutical facilities, you are likely to find that several CIP skids serving various process suites are all located in a central area. The advantage is keeping all the drums with cleaning chemicals and high volume discharges of used solutions to drain away from the classified production areas, as well as simplified maintenance of the CIP equipment. But that also leads to the CIPS and CIPR lines being very long. For example, some of the CIP circuits in the biopharmaceutical facility mentioned at the beginning of this article include more than 600 feet of piping. The hold-up volume in such circuit with 2" diameter tubing is close to 100 gal. That leads to a very high water usage for a CIP cycle involving multiple wash and rinse steps. The long CIP supply and return lines also affect the CIP cycle time: at 50 gpm circulation rate, it will take almost two minutes just to fill the CIP circuit in the example above so each rinse and air blow takes much longer.

Possible Ways to Improve the CIP Design in Large Biopharmaceutical Facilities

As we described above, installing multiple CIP skids serving various areas of a large facility in one central area leads to a dramatic increase in the amount of water, chemicals, energy used, wastewater generated, and cycle time increase due to the long CIP supply and return lines. Considering the current trend to build the larger and larger biopharmaceutical plants, this problem is likely to persist. Although the authors are not aware of any solution that would be perfect in all respects and applicable to any project, here are some options that may be useful.

1. Portable CIP skids.

This approach is not likely to gain wide acceptance in large

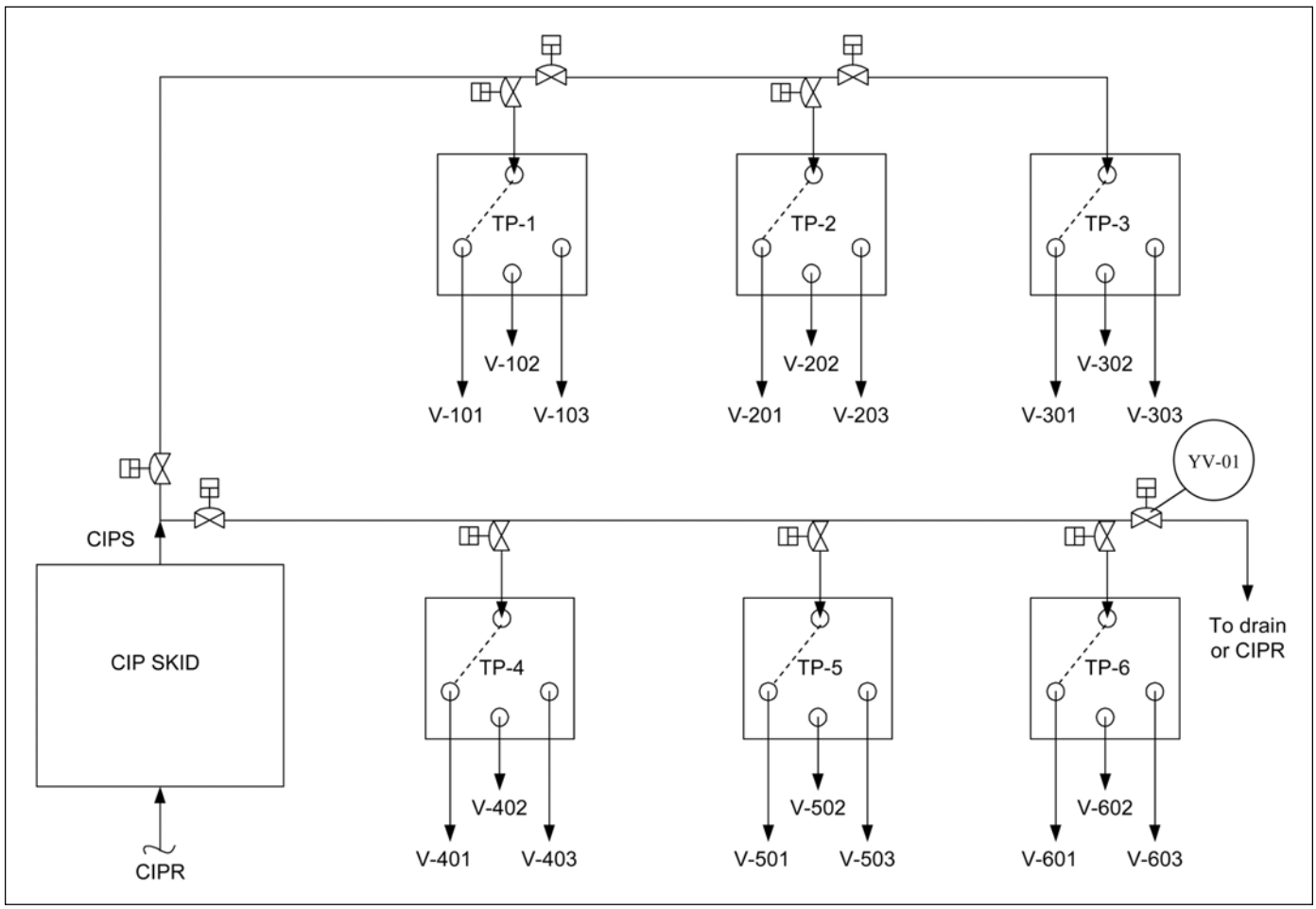

Figure 6. CIP distribution system with valve manifold. Upper header illustrates option with two valves per branch, lower header - with one valve per branch.

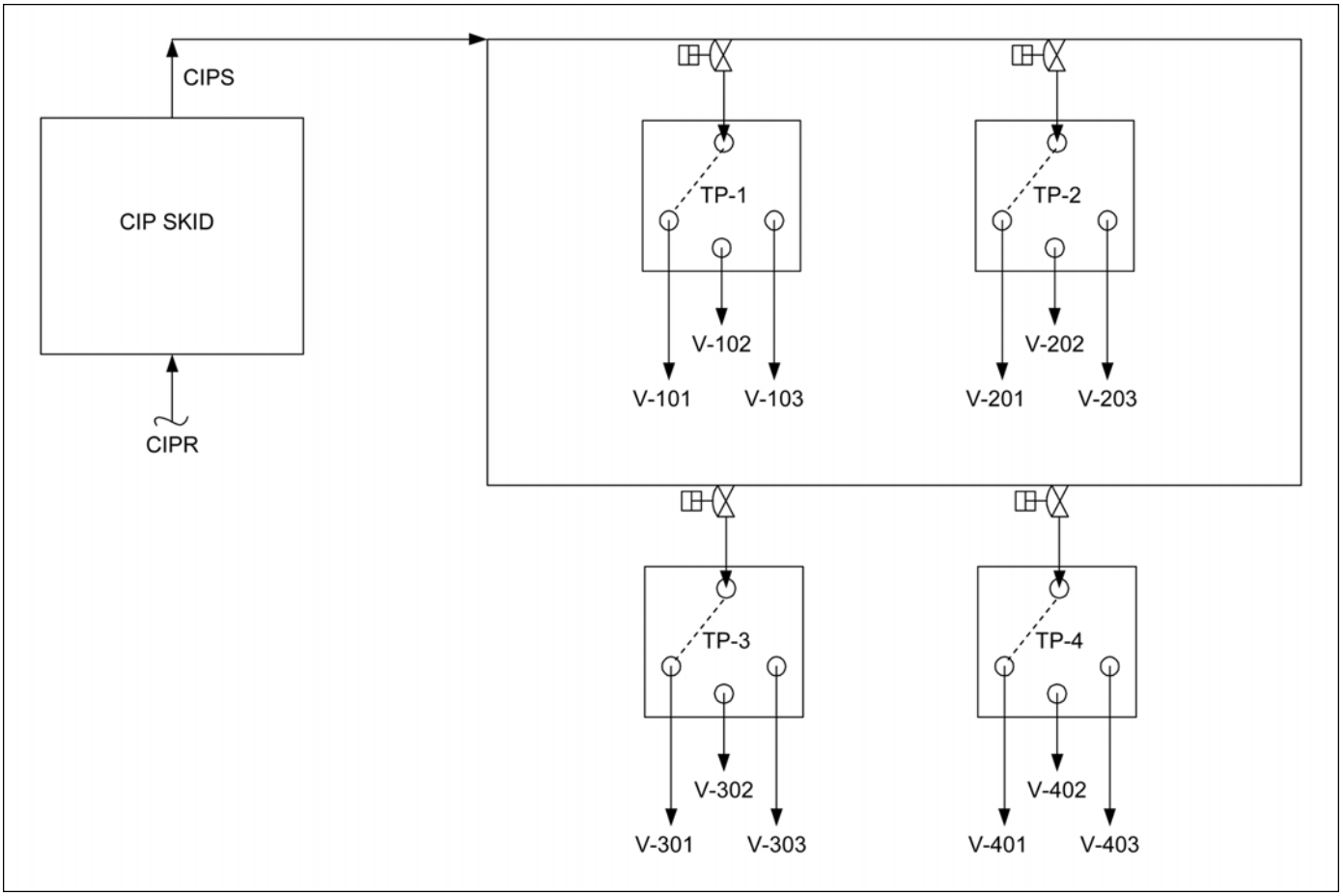

Figure 7. CIP distribution system with loop header.

modern plants for cleaning of major equipment, but it may be useful for cleaning some smaller vessels, especially those that do not need to be cleaned very often. The greatest disadvantages of using a portable CIP skid are the labor intensity and the need to move it between various process areas.

2. Fixed CIP skids installed near or inside the area they serve.

This approach would reduce the usage of water and chemicals for CIP (in almost direct proportion to the average distance from the CIP skid to the process equipment), but may present challenges for the development of the overall facility layout. Since many of the process operations are conducted in the GMP classified areas (Class 100,000, class 10,000 etc.) or in controlled manufacturing areas, it would require special effort to find a suitable place for the CIP skid nearby. On the other hand, we often have to place utility equipment such as temperature control modules or CIP return pumps within close proximity to the process vessels so we should be able to find a space for a CIP skid, especially a small one. And, a CIP skid can be as small as 3' × 5' if we provide the water supply to it at a high flow rate, eliminating the need for on-skid holding tanks. To avoid handling of the drums with cleaning chemicals throughout the building, the bulk storage tanks may be located in the utility area, and the concentrated chemicals may be distributed to various CIP skids. In our opinion, this design approach based on the proper use of conventional recirculated CIP technology shall be seriously considered for new biopharmaceutical facilities.

3. Modify the cleaning recipe for maximum water conservation.

In particular, the customer may collect the final rinse water from one CIP cycle for re-use in the pre-wash step for the next piece of equipment. This approach is widely used in the food and dairy industries, but not in the pharmaceutical industry. The argument commonly made against it is the increased probability of cross-contamination. While we don't find this argument very convincing, most biopharm companies prefer to err on the side of caution and do not re-use the final rinse water.

4. Alternative CIP approach.

This option entails moving away from the concept of a single-use recirculated CIP system that has been the de-facto standard in the industry for many years. Instead, it uses a set of the storage tanks located in a central utility area each holding one of the "standard" cleaning solutions: one tank for diluted caustic, one for diluted acid, one for purified water. Each solution is maintained at required temperature and concentration, and distributed throughout the building like any other utility - *Figure 8*. To clean a piece of equipment, we simply open and close the point of use valves for appropriate

solutions that flow once through to drain. While implementing such approach, it is important to incorporate some measures that would prevent backflow of the cleaning chemicals into the WFI loop. The example in Figure 8 shows the mixproof sanitary valves as one of the means for achieving that goal.

The advantages of alternative CIP design are:

- Less equipment dedicated to CIP may be required. Instead of six CIP skids, each containing two tanks, one pump and one heater, we might have to install only two tanks for diluted chemicals, each with a pump and a heater (that assumes that facility already has a purified water storage tank and recirculation pump).

- No need for the CIP return piping network: all used cleaning solutions go directly to drain. This combined with the item above may lead to the reduced capital cost of the facility.
- Increased operating flexibility. Unlike the traditional approach with dedicated CIP skids where only one piece of equipment in a particular area can be cleaned at any given time (even if five other CIP skids dedicated to other plant areas are sitting idle), this design allows several pieces of equipment to be cleaned simultaneously, regardless of where they are located.

- Reduced risk of equipment cross-contamination. With once-through flow of all cleaning solutions, there is no chance of introducing any would be contaminants from one process tank to another. While the authors believe that the standard recirculated CIP systems do not pose cross-contamination risk in the majority of applications, there are cases where this is a valid concern. For example, as a matter of cGMP, the same CIP skid shall not be used for cleaning of "virus-free" and "virus contaminated" equipment in the cell culture facility. Such concerns would be removed with the once-through CIP design.

- Reduced complexity of the biological containment for the facilities handling hazardous microorganisms. For example, in a Biosafety Level 2 (BL-2) facility, the CIP solutions from a process vessel cannot be recirculated back to the CIP skid unless the skid itself is designed for routine sterilization and is located in a BL-2 containment area. Once-through cleaning eliminates this problem.
- Reduced CIP cycle time. Since all required cleaning solutions are always available at the correct concentration and temperature, there is no need to spend time for their preparation and heating every time we run a CIP cycle. Combined with the shorter time required for each wash and rinse step due to elimination of the long CIP supply and return piping, the overall CIP cycle time reduction can be substantial.

- Reduced usage of water for all rinses. While the amount of chemical solutions used in the proposed once through system would likely be higher than with a typical CIP system (where the chemical wash is normally recirculated), the amount of water required for rinses would be reduced because all rinses are once through in both sys-

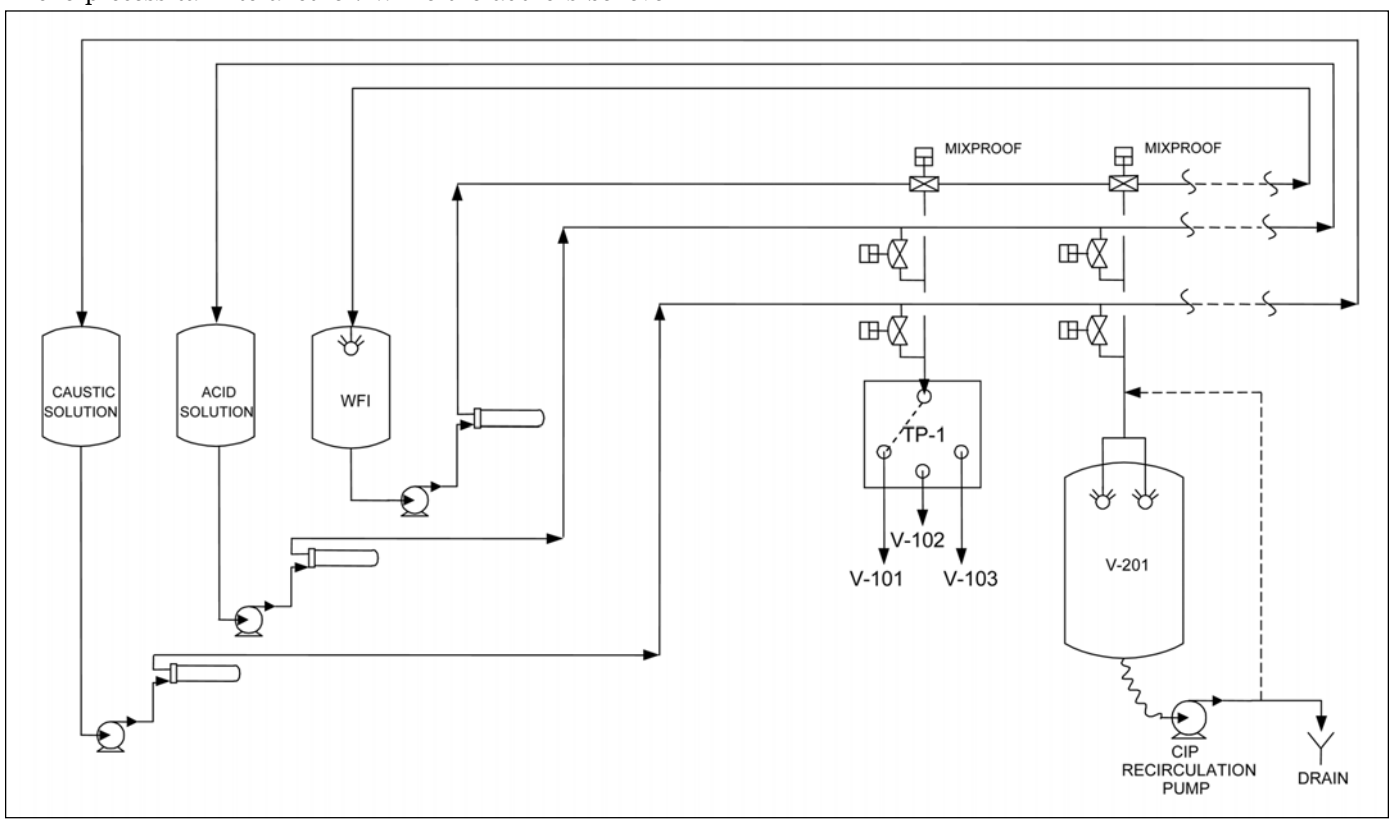

Figure 8. Concept diagram of a plantwide CIP system with separate distribution piping for each of the cleaning solutions.

	Conventional CIP		Alternative CIP scheme		
Step	Time (min)	Volume (gal)	Time (min)	Volume (without local recirculation)	Volume (with local recirculation)
1st rinse	5	250	3	150	150
Caustic wash	15	190	11	550	80
2nd rinse	9.4	470	3	150	150
Acid wash	10	190	6	300	80
3rd rinse	9.4	470	3	150	150
Final rinse	9.4	470	3	150	150
TOTAL	58.2	2040	29	1450	760

The numbers for the step times and solution volumes in Tables A and B are calculated as follows:

For the caustic wash steps: 10 min (minimum contact time), plus 1 min for the branch valves, plus (for conventional CIP only) 2 min to fill the CIP supply/return lines and 2 min to heat up the solution. The volume in conventional CIP equals system volume (which is 100 gal for piping, plus 20 gal in wash tank, plus 20 gal in process tank = 140 gal), plus 1 min flow for branch valves (50 gal for the large or 25 gal for the small vessel).

For the acid wash steps: 5 min (minimum contact time), plus 1 min for the branch valves, plus (for conventional CIP only) 2 min to fill the CIP supply/return lines and 2 min to heat up the solution. Volume is the same as above.

For the first rinse steps: 2 min (minimum rinse time), plus 1 min for the branch valves, plus (for conventional CIP only) 2 min to fill the CIP supply/return lines.

For all other rinse steps: for the conventional CIP the rinse volumes are 3 times the system's volume (3*140 gal), plus 1 min flow for branch valves. For the alternative CIP scheme the rinse volumes are assumed the same as for the first rinse.

Table A. Solutions usage comparison for CIP of a large process vessel.

tems, but in the proposed design the length of the CIP supply and return piping is greatly reduced. The total amount of water per cycle may increase or decrease depending on the required duration of the chemical wash step, length of the CIP supply and return piping (in the standard CIP option), and other factors.

The main disadvantages of this design are the reduced flexibility to modify the recipe (no ability to use chemical solutions at different concentrations and/or temperatures for different pieces of equipment) and higher usage of cleaning chemicals. Another minor disadvantage is losing the ability to monitor the conductivity and temperature of the used CIP solutions normally performed at the CIP skid - *Figure 1*. Instead, a separate conductivity sensor has to be installed at the outlet of each process vessel. Alternatively, conductivity monitoring can be done during CIP validation studies using portable or temporarily installed instruments, and then not used in the day-to-day operations.

This CIP distribution approach may be beneficial for the large facilities with many pieces of equipment that otherwise would be served by multiple CIP skids. In the biopharmaceutical plants it definitely seems very attractive for the buffer hold tanks that are normally cleaned by a WFI rinse. Another likely application would be washing of small vessels or small diameter process lines that use only 10 – 15 GPM of CIP flow. In such cases, a once-through wash operation for five to 10 minutes may actually use less chemical solution than would be used by a conventional CIP system with long CIP supply and return lines. This approach also is useful in cases where once-through CIP operation is dictated by process reasons such as biohazard containment etc.

5. Alternative CIP approach with local recirculation.

To avoid the increased usage of chemicals associated with the Option 4 above, the design can be modified by adding a portable recirculation pump to each large piece of equipment (or to a group of several pieces of equipment) and recirculating the wash solutions locally instead of sending them back to the remotely located CIP skid - *Figure 8*. In most cases, such a pump already exists in the conventional design – the CIP return pump. Essentially, this option is a crossover between Option 4 and the conventional recirculated CIP system. The benefit of reduced chemical usage is achieved in this case at the expense of adding some system complexity and capital cost to Option 4.

Comparison of the Water and Chemical Usage for Various CIP Concepts

In order to quantify the "pros" and "cons" of the various CIP distribution design options discussed above, we estimated how much water and cleaning chemicals are required for a complete CIP cycle of a process circuit, depending on the design option and on the size of process equipment being cleaned. The two main design options compared are the conventional recirculated CIP approach with long distribution lines from the CIP skid to the process equipment, and the "alternative approach" described as Option 4 above. In addition, effect of the local recirculation (Option 5) is also estimated. We considered cleaning of one "large" (6 to 7 feet diameter) and one "small" (3 to 4 feet diameter) vertical tank with associated piping.

Before presenting the results, we would like to emphasize that the "conventional CIP" case considered here refers to the situation where the CIP skid is located very far from the process equipment being cleaned, which creates a major disadvantage for this approach. If it wasn't for that, the comparison with once-through CIP would have looked quite differently.

The following assumptions were made for the estimates:

- distance from the CIP skid (or alternate CIP equipment) to the process vessel is 300 ft
- minimum volume of liquid in the CIP wash tank required to keep the CIP supply pump primed is 20 gal
- residual volume of liquid in the process tank during CIP washes and rinses is 20 gal
- CIP flow rate for the "large" tank is 50 gpm, for the "small" tank is 25 gpm
- CIP distribution (supply and where applicable, return) lines throughout the plant are constructed of 2" sanitary tubing

- the volume of liquid required to fill the CIP supply and return piping for the conventional CIP design is approximately 100 gal
- The cleaning circuit includes some branch valves (such as for example valve YV-01 in Figure 6) that have to be pulsed open during each step of the CIP cycle, diverting the cleaning solution to drain. The total amount of each solution used to flush these branch valves (and therefore not recirculated) is equal to one minute's flow (50 gal for the "large" and 25 gal for "small" vessel).
- minimum contact time required for the caustic wash is 10 minutes, for acid wash – five minutes.
- volume of water required to rinse the previous solution out of the cleaning circuit equals three times the operating circuit volume.
- For the alternative CIP approach (and for the first rinse in the conventional case), the rinse volume for the vessel itself is based on the two minutes time at the design flow rate. That does not include the water required to rinse the branch valves or to fill the CIP supply/return lines.

Tables A and B represent the results of our estimates for the "large" and "small" vessel CIP respectively.

As can be seen from Table A, an alternative CIP approach may lead to an overall reduction of the water used for the CIP cycle, even though the usage of chemical solutions increases compared to the conventional recirculated CIP design. Incorporating local recirculation of the wash solutions in the process vessel can help in reducing the water and chemical usage much further. The CIP cycle time is substantially shorter with the alternative CIP distribution design because time is not spent filling up the long supply and return lines, heating up the wash solutions to required temperature, or rinsing the wash solutions out of those long lines. In fact, the cycle times for the conventional CIP case tend to be even longer than shown here because we didn't allow for the time spent filling up the wash and rinse tanks on the CIP skid, as well as for the cleaning circuit set-up time.

The results of the small vessel CIP simulation presented in Table B are somewhat similar, except that the savings in water usage and in the cycle time achieved with the alternative design approach are even more pronounced. In fact, we may notice that with conventional recirculated CIP, the amount of water used is almost independent of the scale of equipment being washed (1840 gal for a small versus 2040 gal for a large vessel). That highlights the fact that with the long CIP distribution lines, most of the water is essentially used to wash and rinse those lines rather than the process equipment itself. And, due to the reduced CIP flow rate, the cycle time for cleaning a small vessel by conventional recirculated CIP skid is much longer than that for cleaning of a large vessel. The alternative CIP distribution design overcomes these problems by bringing each of the necessary CIP solutions to the process equipment in a separate line, leaving only a very short section of CIP supply pipe (from the point-of-use valve to the spray ball) that needs to be rinsed at every step.

It may be prudent to point out that any savings in the usage of water and cleaning chemicals achieved by modifying the CIP design approach is likely to cause a corresponding reduction in the energy usage (plant steam, chilled water, electrical power), and in the wastewater generation.

	Conventional CIP		Alternative CIP scheme		
Step	Time (min)	Volume (gal)	Time (min)	Volume (without local recirculation)	Volume (with local recirculation)
1st rinse	7	175	3	75	75
Caustic wash	17	165	11	275	55
2nd rinse	17.8	445	3	75	75
Acid wash	12	165	6	150	55
3rd rinse	17.8	445	3	75	75
Final rinse	17.8	445	3	75	75
TOTAL	89.4	1840	29	725	410

Table B. Solutions usage comparison for CIP of a small process vessel.

Effect of the CIP Design Concept on the Facility's Capital Cost

Selection of one or another approach with regard to CIP equipment may affect not only the facility's operating factors such as water, chemicals, and energy usage, but also the amount of CIP-related equipment and piping required, and therefore capital cost of the plant. To get a general idea of how the capital cost may be affected, we compared order of magnitude costs of the CIP-related equipment and piping for two hypothetical design cases - *Table C*. For this exercise, we assumed that a large biopharmaceutical facility requires six conventional CIP skids to clean all process equipment and estimated the total length of CIP supply and return piping at 9,000 ft (the piping length estimate is based on the author's experience with an actual design of similar plant). For the

Description	Quantity	Units	Unit Cost	Subtotal
Conventional CIP with 6 skids				
CIP skid (installed cost)	6	each	$ 500,000	$ 3,000,000
CIP supply/return piping	9000	feet	$ 300	$ 2,700,000
Total				*$ 5,700,000*
Alternative CIP				
Caustic tank skid (installed)	1	each	$ 300,000	$ 300,000
Acid tank skid	1	each	$ 300,000	$ 300,000
Caustic distribution piping	3000	feet	$ 150	$ 450,000
Acid distribution piping	3000	feet	$ 150	$ 450,000
WFI piping (incremental portion)	2000	feet	$ 300	$ 600,000
Total				*$ 2,100,000*

Table C. Order of magnitude cost comparison of conventional and alternative CIP distribution concepts.

alternative CIP design, we assumed that six automated CIP skids could be replaced with two simple (and less automated) skids, one containing holding tank and recirculation pump for the diluted caustic solution, and another – for acid solution. We also assumed that the distribution piping for those two solutions is made out of general purpose stainless steel pipe rather than more expensive sanitary tubing typically used for the CIP supply and return. As for the Water-For-Injection, each biopharmaceutical facility has a distribution system for it in any case, but in order to implement the alternative CIP concept, the system needs to be expanded so we made an allowance for the 2,000 feet of extra tubing.

While the numbers in Table C are just crude estimates and shall not be taken too seriously, they illustrate the argument that in certain (not all!) cases, an alternative approach to the CIP equipment may lead to a reduction of the overall facility's cost in addition to other benefits.

Conclusion

Based on the amount of attention given in the preceding paragraphs to the "Alternative CIP concept," the reader might have gotten an impression that the authors recommend it over all other design concepts in most cases. If so, that would be a wrong impression. The alternative concept exhibits clear benefits in water and cycle time savings in our comparison with conventional CIP approach only because the conventional CIP case considered in that comparison is far from optimal. Each of the design schemes would work well when used for the right applications. More than that, the options described above do not constitute a comprehensive list of CIP design solutions. None of them is appropriate for all facilities or for all types of equipment. There may be many innovative ways to design biopharmaceutical facilities in general and the CIP systems in particular. Even a simple increase in the facility physical size and number of equipment pieces may lead to quite a different design concept for CIP. The main purpose of this article is to stimulate "out of the box" thinking when dealing with the CIP issues. It is likely that an optimum CIP design for a particular facility would include a combination of several design concepts.

For further reading on various issues related to equipment CIP, please refer to the following publications.[4-10]

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This article summarizes and clarifies terms and issues related to the vacuum integrity testing of lyophilizers.

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The Vacuum Integrity Testing of Lyophilizers

by Charles D. Dern, PE

Introduction

Referencing equipment that manufactures Large Volume Parenterals (LVPs), the current Good Manufacturing Practices (cGMPs) state that: "Equipment shall be constructed so that contact components, including process materials, drug products, or the drug product contact area of containers or closures, shall not affect the safety, identity, strength, quality, or purity of the Large Volume Parenteral drug product."[1] Because of the nature of the vapor pressure of ice, both the primary and secondary drying phases of the lyophilization cycle must take place in a vacuum in order to effect the sublimation and desorption of water or other solvent out of the product. In turn, because the lyophilization process occurs in an evacuated vessel, both designers and users of lyophilizers are presented with unique challenges in maintaining the sterility of the product in a vacuum. Among these challenges are the measurement of system "tightness" and the establishment of an inleakage criterion that maintains a reasonable assurance of product sterility. With this in mind, the Vacuum Integrity Test is an important part of any Factory Acceptance Test (FAT), Site Acceptance Test (SAT), and/or Operation Qualification (OQ).

Figure 1. A Typical research lyophilizer.

Basic Definitions

Before exploring practical issues, some basic definitions are essential. One can measure the relative tightness of evacuated vessels by one of two criteria: "rate of rise" or "leak rate." Rate of rise is the amount of pressure change in an evacuated vessel over a given period, e.g., milliTorr per minute (mTorr/min) or milliBar per second (mBar/sec).[2] For example, if one evacuates a vessel to 100 mTorr (0.133 mBar), closes the isolation valve to the vacuum pump, and then observes that after one minute, the pressure is 102 mTorr (0.136 mBar), then the rate of rise is quite simply 2 mTorr per minute (0.003 mBar/min). Mathematically the formula is:

$$\textbf{Rate of Rise} = \frac{\text{Finish Pressure - Start Pressure}}{\text{Elapsed Time}}$$

However, rates of rise, no matter how carefully done, are not an accurate basis for comparing tightness among vessels of various sizes. This is because rates of rise do not account for the volumes of the vessels in question. If a 10 ft^3

Volume: Liters	Volume: Feet^3	mBar/ minute	mTorr/ minute	Volume: Liters	Volume: Feet^3	mBar/ minute	mTorr/ minute
50	1.77	1.20E-02	9.023	3600	127.12	1.67E-04	0.125
60	2.12	1.00E-02	7.519	3700	130.65	1.62E-04	0.122
70	2.47	8.57E-03	6.445	3800	134.18	1.58E-04	0.119
80	2.82	7.50E-03	5.639	3900	137.71	1.54E-04	0.116
90	**3.18**	**6.67E-03**	**5.013**	**4000**	**141.24**	**1.50E-04**	**0.113**
100	3.53	6.00E-03	4.511	4100	144.77	1.46E-04	0.110
200	7.06	3.00E-03	2.256	4200	148.31	1.43E-04	0.107
300	10.59	2.00E-03	1.504	4300	151.84	1.40E-04	0.105
400	14.12	1.50E-03	1.128	4400	155.37	1.36E-04	0.103
500	**17.66**	**1.20E-03**	**0.902**	**4500**	**158.90**	**1.33E-04**	**0.100**
600	21.19	1.00E-03	0.752	4600	162.43	1.30E-04	0.098
700	24.72	8.57E-04	0.644	4700	165.96	1.28E-04	0.096
800	28.25	7.50E-04	0.564	4800	169.49	1.25E-04	0.094
900	31.78	6.67E-04	0.501	4900	173.02	1.22E-04	0.092
1000	**35.31**	**6.00E-04**	**0.451**	**5000**	**176.55**	**1.20E-04**	**0.090**
1100	38.84	5.45E-04	0.410	5500	194.21	1.09E-04	0.082
1200	42.37	5.00E-04	0.376	6000	211.86	1.00E-04	0.075
1300	45.90	4.62E-04	0.347	6500	229.52	9.23E-05	0.069
1400	49.44	4.29E-04	0.322	7000	247.18	8.57E-05	0.064
1500	**52.97**	**4.00E-04**	**0.301**	**7500**	**264.83**	**8.00E-05**	**0.060**
1600	56.50	3.75E-04	0.282	8000	282.49	7.50E-05	0.056
1700	60.03	3.53E-04	0.265	8500	300.14	7.06E-05	0.053
1800	63.56	3.33E-04	0.251	9000	317.80	6.67E-05	0.050
1900	67.09	3.16E-04	0.237	9500	335.45	6.32E-05	0.047
2000	**70.62**	**3.00E-04**	**0.226**	**10000**	**353.11**	**6.00E-05**	**0.045**
2100	74.15	2.86E-04	0.215	10500	370.76	5.71E-05	0.043
2200	77.68	2.73E-04	0.205	11000	388.42	5.45E-05	0.041
2300	81.21	2.61E-04	0.196	11500	406.07	5.22E-05	0.039
2400	84.75	2.50E-04	0.188	12000	423.73	5.00E-05	0.038
2500	**88.28**	**2.40E-04**	**0.180**	**12500**	**441.38**	**4.80E-05**	**0.036**
2600	91.81	2.31E-04	0.174	13000	459.04	4.62E-05	0.035
2700	95.34	2.22E-04	0.167	13500	476.69	4.44E-05	0.033
2800	98.87	2.14E-04	0.161	14000	494.35	4.29E-05	0.032
2900	102.40	2.07E-04	0.156	14500	512.01	4.14E-05	0.031
3000	**105.93**	**2.00E-04**	**0.150**	**15000**	**529.66**	**4.00E-05**	**0.030**
3100	109.46	1.94E-04	0.146	16000	564.97	3.75E-05	0.028
3200	112.99	1.88E-04	0.141	17000	600.28	3.53E-05	0.027
3300	116.53	1.82E-04	0.137	18000	635.59	3.33E-05	0.025
3400	120.06	1.76E-04	0.133	19000	670.90	3.16E-05	0.024
3500	**123.59**	**1.71E-04**	**0.129**	**20000**	**706.21**	**3.00E-05**	**0.023**

Table A. Equivalent rates of rise of given volumes for a leak rate of 1 × 10-2 mBar-L/sec.

(2831 L) vessel and a 100 ft^3 (2831 L) vessel have the same rate of rise, a greater amount of gas must leak into the 100 ft^3 vessel to raise the pressure the same amount, in fact, 10 times as much. To do an accurate comparison, therefore, one must account for the respective volumes of the vessels. This is accomplished by a "leak rate." Obtaining a leak rate involves multiplying "rate of rise" by the system volume. Thus, if a rate of rise is expressed in millitorr per minute (mTorr/min.), then a leak rate is expressed as millitorr × cubic feet per minute (mTorr-ft^3/min.) The general formula is:

$$\textbf{Leak Rate} = \frac{(\text{Finish Pressure} - \text{Start Pressure}) \times \text{Volume}}{\text{Elapsed Time}}$$

or

$$\textbf{Leak Rate} = \text{Rate of Rise} \times \text{Volume}$$

For example, assume that vessels of 10 ft^3 and 100 ft^3 both are evacuated to 100 mTorr (0.133 mBar) and are maintained at a constant temperature. At this pressure, the 10 ft^3 vessel will contain 0.00132 standard cubic feet (SCF) (0.037 L) of gas and the 100 ft^3 vessel will contain 0.0132 SCF (0.37 L) of gas. Assume further that each vessel has an identical leak that allows 0.001 SCF (0.028 L) of gas in one minute into each vessel. At the end of one minute:

- The 10 ft^3 vessel contains 0.00232 SCF (0.066 L) of gas and is at a pressure of 176 mTorr (0.235 mBar) for a rate of rise of 76 mTorr/min (0,101 mBar/min).

- The 100 ft^3 vessel contains 0.0142 SCF (0.40 L) of gas and is at a pressure of 107.6 mTorr (0.143 mBar) for a rate of rise of 7.6 mTorr/min (0.0101 mBar/min).

Both chambers have the same leak yet the smaller chamber has the greater rate of rise. However, if the rates of rise are multiplied by the respective chamber volumes, one obtains:

10 ft^3 × 76 mTorr/min = 760 mTorr-ft^3/min
(283.1 L × 0.101 mBar/min = 28.6 mBar-L/min)

and

100 ft^3 × 7.6 mTorr/min =760 mTorr-ft^3/min
(2831 L × 0.0101 mBar/min = 28.6 mBar-L/min)

The vessels have identical leak rates. Even though the 100 ft^3 vessel has 10 times the evacuated volume of the 10 ft^3 vessel, as long as the vessels are at the same pressure and have identical leaks, virtually the same amount of gas will enter into each vessel over a limited range. This is because the orifice of each leak "sees" approximately the same suction.[3] The obvious advantage of leak rate over rate of rise is that those who own lyophilizers of various sizes can specify a single master acceptance criterion (although the actual test requires that one measure a rate of rise). Figures 1 and 2 of research and production lyophilizers respectively, show just how size can vary among systems. Yet, despite their size differences, both systems can reasonably be held to the same leak rate criterion.

Testing for Vacuum Integrity

The actual testing for vacuum integrity is the same time straightforward and not so straightforward. It is straightforward in that the basic test sequence is simple: chill condensing plates (to protect vacuum pumps), evacuate system, stop evacuation, allow system to stabilize, and measure rate of rise. It is not so straightforward for several reasons: the problem of "real leaks" and "virtual leaks," the influence of system temperature, and the lack of an industry-established acceptance criterion.

Real Leaks

Real leaks can be difficult to locate, but once located often are fixed easily. Location of leaks can be done with equipment as sophisticated as a Helium Leak Detector, or simply by pressurizing the system, coating seal surfaces with soap, and watching for bubbles (although some seals that leak under vacuum may not leak under pressure).[4] On external condenser systems with a main vapor valve, one can close this valve and isolate the chamber from the condenser, and check each vessel for leaks separately. Multiple stoppering rod ports of some older freeze dryers are a notorious source of real leaks. Other common points for inleakage include door seals, main vapor valve flanges, instrumentation connections, thermocouple leadthroughs, relief valves, and process valves.

Virtual Leaks

A major concern for those performing vacuum integrity tests is the presence of what are called virtual leaks. As the name implies, virtual leaks are not real or actual leaks caused by a breach in the vessel's walls or seals. Outgassing materials or gas pockets contained within the vessel can cause a greater rate of rise than one would otherwise obtain. In such a case, one can be led to believe that there is a defect in the vessel's physical structure when in fact there is not. One indication of virtual leak is a decrease in the rate of rise over time. As Figure 3 illustrates, when a virtual leak is present, the rate of rise will taper off as time progresses.

One cause of virtual leaks is humidity and/or fluids within the vessel. If the vessel to be tested is not clean, dry and empty, pressure increases caused by the vaporizing of water and/or solvents (such as from cleaning) contained within the vessel can occur. As the fluids vaporize, the pressure within the vessel increases at least in part owing to the vaporization and not because of any real problem with the system. Water trapped in the chamber and/or condenser drain is a very common source for this type of virtual leak. As the system pressure decreases, water trapped in the drain (upstream of the isolation valve) begins to evaporate. However, the process of evaporation requires energy. This energy comes in the form of a temperature reduction of the standing water, a phenomenon called "evaporative cooling." If enough energy leaves the standing water, the water will freeze, and cause a virtual leak as it slowly sublimates. One field technician's trick to detect this problem is to feel the drainpipe. If the pipe is rather cold to the touch, then one likely has water in the drain.

Second, the outgassing of volatiles from polymers and/or other substances can have a similar effect. As in the first case, volatiles will leach out of polymers (such as seals) until the vapor pressure of the volatile equalizes with the system pressure.

A third type of virtual leak occurs when air (or other gas) is trapped in an annular space that has no opening to the outside of the vessel and a relatively small opening to the inside (e.g. a cavity within a weld). While the main vessel

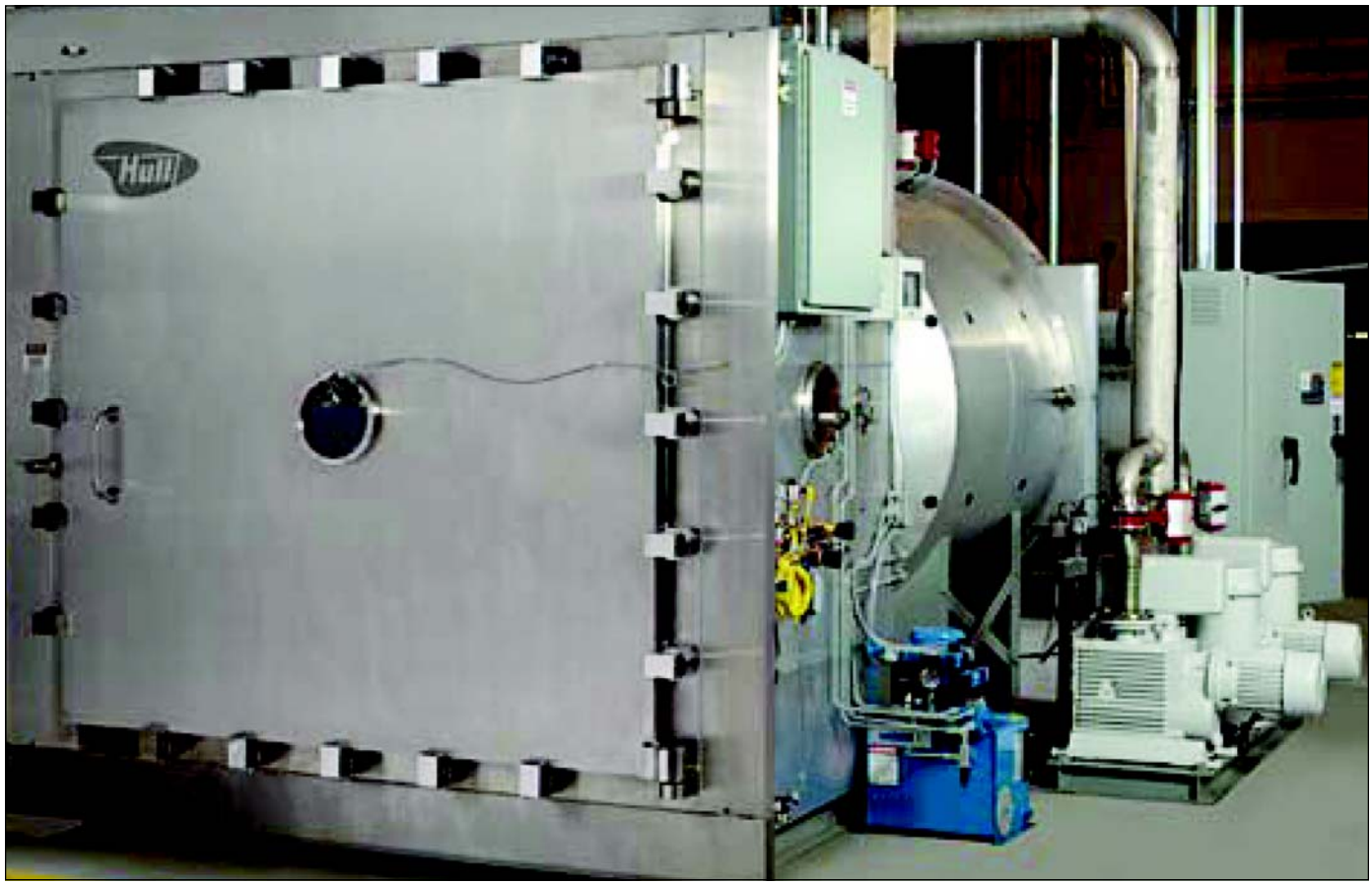

Figure 2. A Typical production lyophilizer.

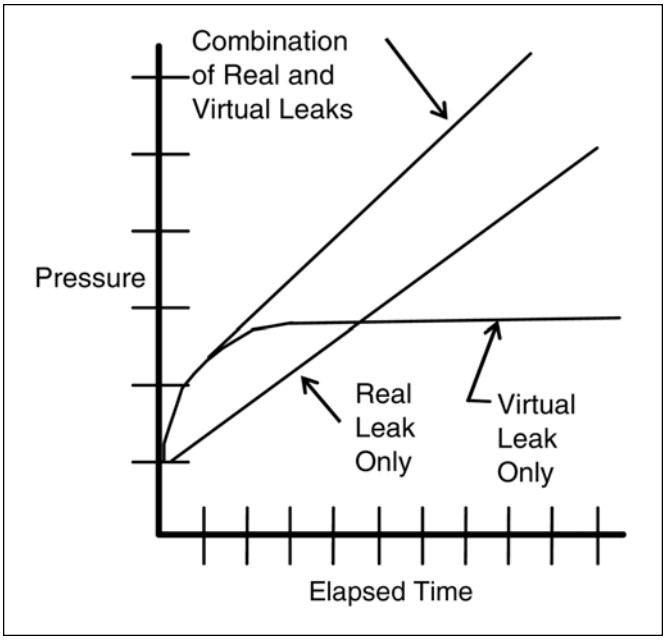

Figure 3. Real and virtual leak plots.

evacuates rather quickly, the gas trapped in the annular space evacuates much more slowly. Thus, while the vessel will appear to have been evacuated to the desired pressure, higher pressure gas will remain trapped in the annular space. When a leak rate or rate of rise measurement is attempted, a false reading will occur because of the gradual leakage of the gas from the annular space into the main vessel.

A properly constructed vessel, especially a vessel certified for positive pressure, should not have any voids, particularly in the welds. In addition, seals made of polymers with vapor pressures lower than the process parameters should be used. EPDM, silicone, and viton work well in vacuum applications and also withstand exposure to steam during a sterilization cycle. Still, only trial and error experimentation can determine if virtual leaks are present. If one suspects a virtual leak, a possible remedy is to evacuate the vessel for an extended length of time. This will allow some vapors to be driven off outgassing substances and/or time for gases to evacuate from annular spaces.

Temperature, Pressure, and Time Considerations

The combined gas law (PV=nRT) tells us that temperature and pressure are inextricably related. Because a system evacuated to the freeze drying range (50 to 300 mTorr, or 0.067 to 0.40 mBar) contains so little gas, and the unit of measure (mTorr or mBar) is so small, small fluctuations in system temperature cause significant variations in readings and results. Fortunately, lyophilizers have shelves with controllable temperatures and condensing plates, which if operating properly, will bottom-out at a consistent temperature (about -95°F (-70°C) for two-stage systems using refrigerant R507). England's Parenteral Society recommends that freeze-dryer shelves be maintained at +104°F (+40°C) to encourage outgassing while the condenser is kept at -40°F (-40°C) or colder to protect the vacuum pumps.[5] Common practice in the United States is to keep the shelves at or below ambient (68°F or 20°C) while allowing condensing plates to attain their minimum temperature.

One caveat, the lyophilizer's refrigeration system can mask virtual leaks. If a surface within the evacuated vessel is cold enough such that outgassing volatiles condense onto it, the effect of a virtual leak can be reduced if not completely abrogated. (Most of the components of air, except water vapor, are non-condensable. As such, the refrigeration system minimally affects real leaks.) Foremost, as long as one maintains consistent temperatures from test to test, one will have comparable results. Furthermore, it is inaccurate to compare the leak rate of a vessel performed without refrigeration to the leak rate of vessel performed with refrigeration.

The pressure at which one performs a Vacuum Integrity Test is also a critical parameter. Rates of rise can be performed at any pressure below the local ambient pressure and can be done for any length of time. The best pressure at which to test is at the expected working pressure of the vessel, usually 100 mTorr (0.133 mBar) for lyophilizers. Specifying start pressures well below that of the system's normal operational parameters is unnecessary and potentially costly for several reasons. Components that satisfactorily contain vacuum at the operating condition can fail at the test condition. In addition, volatiles in substances that do not outgas at the operating condition may do so under the test condition. As such, one can expend large amounts of time, money, and effort attempting to solve a "problem" which does not exist at actual operating conditions. Furthermore, lower pressures cause a greater suction through leaks than higher pressures. Therefore, one should expect lower leak rates and rates of rise at lesser vacuums (higher pressures) and higher leak rates and rates of rise at higher vacuums (lower pressures). In fact, one can obtain a rate of rise or leak rate of "0" with any chamber at local ambient pressure.

Time is the third critical factor. In most cases, the longer the elapsed time, the more assurance one will have of obtaining an accurate result. This is especially true for very tight systems. In such systems, the rate of rise can be so slow as to be beyond the measuring accuracy of even a vacuum head with a 1 mTorr resolution. Rate of rise times of one hour or longer allow the measurement of start and end pressures with increased accuracy.

What is an Acceptable Inleakage Criterion?

First, one must verify whether the leak rate specification is for a complete assembled system or for the individual post-fabricated, but pre-assembled chamber or condenser. An assembled system has many more surfaces to which water can cling, as well as more seals exposed to the surroundings. Second, leak rates are most commonly specified in units of milliBar × Liter per second (mBar-L/sec). The Parenteral Society specifies a leak rate of 2×10^{-2} mBar-L/sec "for a new, clean empty freeze dryer."[6] The current, most frequently specified leak rate for new laboratory and production dryers is 1×10^{-2} mBar-L/sec (see Table A for equivalent rates of rise

for given volumes for this leak rate). This author has found acceptance criteria in practice as high as 15 mTorr/min for a mid-sized freeze dryer. Assuming a system volume of 3,000 liters, this translates to a leak rate of 1 mBar-L/sec or, in other words, a tightness spec 100 times that of the current standard for new lyophilizers.

Yet, experience shows that even lyophilizers with leak rates as high as 1 mBar-l/sec apparently produce product with an acceptable sterility. There are several likely reasons for this. First, because the various molecules that make up air are orders of magnitude smaller than microorganisms, one can have inleakage without contamination. If a system has multiple leaks all of whose paths are less than the diameter of a microorganism, one could have a relatively high leak rate, but still have sterility. Second, leaks through the chamber door seal from a sterile core are inconsequential as long as the leaks are not so large as to prevent a system from obtaining the required process vacuum levels. Third, because the lyophilization process involves the outflow of vapor from the vials, it is statistically improbable that a microorganism would flow "backwards" into a vial. Such an occurrence is even more improbable if the leak is at some point in the vapor path downstream from the vials. Finally, one might observe that larger systems are inherently more sterile because there is more volume to "soak up" microorganisms.

Nonetheless, there is a glaring lack of scientific justification for any of the aforementioned numbers. The Parenteral Society gives no rationale for its number of 2×10^{-2} mBar-L/sec. The current standard of 1×10^{-2} mBar-L/sec for new lyophilizers ostensibly came about as a reasonably obtainable minimum. To determine a leak rate that absolutely would prevent the ingress of microorganisms, one must first consider that potential contamination can occur only if a system has at least one leak path that is large enough to pass a microorganism. The only possible guarantee that no microorganism could enter a system is to test to a leak rate that one would obtain for a single leak path orifice, slightly smaller than the smallest undesirable microorganism.[7] Still, even upon calculation of this inleakage rate, it remains difficult to determine whether one has multiple small leaks, each of which is too small to allow the passage of a microorganism, or some smaller amount of larger leaks, each of which is of sufficient size to pass a microorganism.

Conclusion

- The Vacuum Integrity Test is an integral part of the quality assurance of lyophilized parenterals.
- Nonetheless, there are many factors of which one needs to be aware when performing this qualification, such as the influences of time, temperature, start pressure, and virtual leaks.
- To compare vacuum integrity of vessels, one must have the same temperature, pressure, and time conditions. If the volumes of the vessels are dissimilar, then one must specify a volume-based leak rate.
- Current criteria for acceptable vacuum tightness have not been scientifically justified; however, current practices apparently yield acceptably sterile product.

References

1. 21 CFR Part 212 §67.
2. A common vernacular equivalent to milliTorr is "micron." However, "micron" is ambiguous because it also can refer to 1/1000th of an inch. A milliTorr is 1/760,000th of a standard atmosphere and is the unit most commonly indicated on new lyophilization equipment in the United States. On the other hand, the International Society for Lyophilization - Freeze Drying has issued a standard that calls for vacuum units to be specified in Pascals (Pa). See http://www.islyophilization.org/Html/Standards_Report.html, September 2, 2003. See also Thomas A. Jennings, "Standard Leak Rate for a Freeze-Dryer," *Insight*, June 2000, Vol. 3, No. 6.
3. In theory, however, the smaller vessel in the example likely would see a slightly lower leak rate because its pressure rises more quickly, and thus, its "suction" through the leak reduces more quickly.
4. Of course, one must never exceed the pressure rating of the vessel.
5. The Parenteral Society, *Technical Monograph No.7: Leak Testing of Freeze Dryers*, (Wilshire, England: The Parenteral Society, 1995), 7.
6. *Technical Monograph No. 7*, 9.
7. As a favor to this author, Dr. Narlin Beaty, Chief Technical Officer for Chesapeake Biological Laboratories in Maryland, calculated that a 0.2 micrometer orifice (the standard orifice for sterile filtration), with one atmosphere (760 Torr) on one side and full vacuum on the other, will pass approximately 1.51×10^{-10} moles of air per second at 68°F (20°C) or 7.7×10^{-9} ft3/min ($2{,}18 \times 10^{-7}$ L/min).

About the Author

Charles D. Dern, PE, is a Development Application Engineer for SP Industries (Hull and Virtis Freeze Dryers). He has more than 16 years of experience in all aspects of the design of pharmaceutical lyophilizers. He received his BS in mechanical engineering from Drexel University, located in Philadelphia, and has been a Licensed Professional Engineer in the commonwealth of Pennsylvania since 1993. In addition to his membership in ISPE, he is a member of the American Society of Heating, Refrigeration, and Air-Conditioning Engineers (ASHRAE), and the International Society for Lyophilization - Freeze-Drying (ISL-FD). Dern has lectured on fundamentals of lyophilization and performed customer training on freeze dryer operation at locations throughout the US and Puerto Rico and has been invited to speak in Europe. He has authored numerous "Tech Briefs" for SP Industries' Hull division Web site on various topics such as leak rate, surface finishes, and cold loading considerations. In addition, he shares a US patent for the invention of the "Rotary Disk Valve," developed to replace butterfly and poppet-type main vapor valves used in large lyophilizers. He can be contacted by e-mail: chuck.dern@spindustries.com.

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Country Profile

A look at the Pharmaceutical Industry in

BRAZIL

Produced in collaboration with ISPE Brazil

ISPE
Engineering Pharmaceutical Innovation

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Dear ISPE Member,

Having a population of approximately 180 million inhabitants, Brazil is a country of large territorial extensions with different regional characteristics and huge coastlines that offer tourism during the whole year. Brazil also has economic centers with many of the world's major corporations.

Brazil has shown a stable economic panorama in the last 10 years with a controlled inflation level which has led to some big investments in the industrial sector.

In spite of the world's recession, Brazil has been appearing in the news reknowned for its representation in Latin America as well as countries in development.

The Brazilian pharmaceutical industry in particular has shown a good profit level and growth over the last several years.

Forecasters are predicting a 3% increase in the Gross Domestic Product (GDP) and the industries and trade are preparing for this increase in consumer demand.

The national pharmaceutical companies have found a strong and important partnership within the international capital, which is very important to the multinational companies that wish to manufacture and distribute their products in this market worth almost $ 6.5 billion. The local and international partnerships have offered to both sides a great opportunity for the country's development, expertise, and market growth.

In Latin America, Brazil has modern and well prepared industries able to meet the international demands, producing locally and meeting the needs of the whole continent.

Brazil is a country whose population is famous for its hospitality and is happy to invite you to visit. We hope you get delighted to see all the wonderful things that a tropical country can offer you.

Silas Teles Filho

Silas Teles Filho
President, ISPE Brazil Affiliate
2000 - 2004

This feature in *Pharmaceutical Engineering* is designed so that you can tear it out, three hole drill (if desired), and keep it with other Country Profiles as they are published.

Look for the Country Profile on Canada in the March/April issue of *Pharmaceutical Engineering*.

A View of the Brazilian Pharmaceutical Industry

by Antônio Costa, ex. Altana Pharma Market Research and GRUPEMEF (Pharmaceutical Market Researcher Group)

Brazil is a country of large territorial extension (8,547,403 km^2) full of cultural and economic diversities that cause a huge contrast in regional and economic habits. It has a pharmaceutical industry complex with 239 companies. Out of those, 178 are Brazilian and most of the big companies are situated in the south and southeast zones, mainly in two states, São Paulo and Rio de Janeiro.

The industrial development is linked to the state and metropolitan government actions that have increased fiscal incentives in order to get the installation of new plants.

The estimated billing for 2004 is of $5.5 billion to sales of 1.3 billion units. From this billing, 36% come from Brazilian companies, 23% from American companies, 16% from German companies, and 11% from Swiss companies - *Table A and Figures 1-3*.

From the total of the pharmaceutical market, approximately 21% of the billing comes from the Over the Counter (OTC) section.[1]

Generic drugs as well as products containing phytotherapeutic agents have grown considerably in the last five years. The generic products growth is due to governmental policy of costs reduction which currently represents 7.3%. The phytotherapeutic agents have gained market share due to favorable factors such as growing acceptance of doctors and patients and profitability, resulting in higher investments by the industries in this sector.

The phytotherapeutic products, historically dominated by German companies, are currently receiving a lot of investments within the national companies such as Laboratories Aché (the largest Brazilian Company) as well as other companies that work exclusively in this area such as Herbarium and Flora Medicinal (now Natura cosmetics). This sector should grow an average of 10% a year.

This sector has received academic as well as local industrial attention due to the large diversity in Brazilian flora, mainly in the north and northeast regions, where there are many different medicinal plants.

Companies	Share (%)
Laboratórios Aché *	6.28
Aventis Pharma	5.76
EMS Sigma Pharma *	5.47
Novartis	4.72
Roche	4.48
Boehringer Ing	4.32
Schering do Brasil (AG)	3.88
Schering Plough	3.53
Medley *	3.44
Pfizer	3.25
* Brazilian Companies	

Table A. Ten main laboratories in billing.

As one of the most important centers of exportation in Latin America, Brazil shows a growth expectation of 10% in relation to last year; a period which has ex-

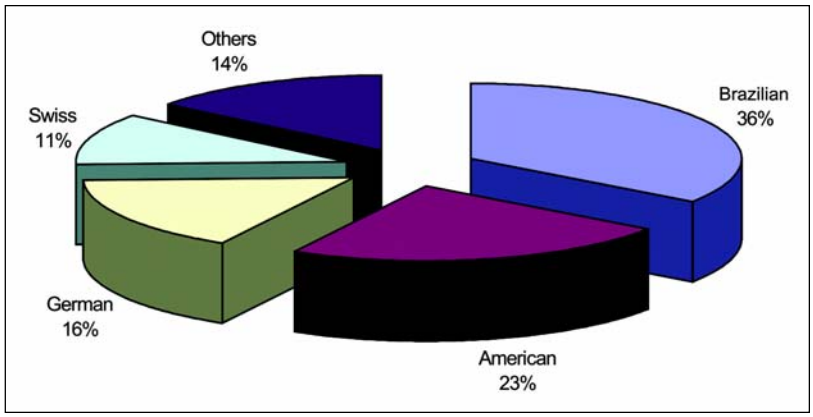


Figure 1. Market share (USD) by country.[3]

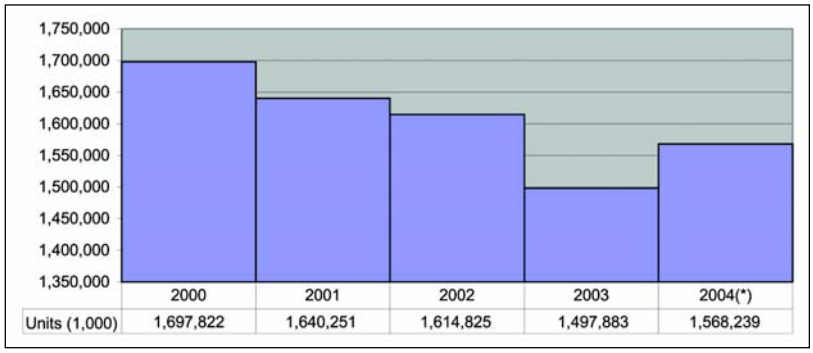


Figure 2. Brazilian pharmaceutical market in units (1,000).[1]

Continued on page 5.

Research and Development

by Carlos A. Morales Paris, MD, Apsen Pharmaceutical Medical and R&D Director

Since the mid '90s, the Brazilian pharmaceutical industry has invested $2 billion in the building, modernization, expansion of production lines resulting in the introduction of top products and an increase of scale and productivity (FEBRAFARMA).

Due to the high competition and the tough rivalry among the manufacturers in the country, approximately 2,000 new drugs have been launched in the last seven years.

A relevant event was the introduction of generic named drugs to the Brazilian market in 1999. It generated the availability of 4,500 equivalent drugs. It not only increased the variety of drugs in the market, but also gave the consumer the option of having cheaper products with the same quality of the known brands.

This initiative received investments of R$ 1 billion reais in building and modernizing the plants. It directly created 10 thousand new jobs and resulted in the opening of 20 new laboratories specialized in bioequivalence tests

The pharmaceutical industry invests the equivalent of 21% of the sales in Research and Development, four times more than in the sectors traditionally associated with modern technologies, such as automobiles, electronics and telecommunications.

This demonstration of technological, managerial, and market capacity is still more important since the pharmaceutical industry in the country is doing well in an adverse economic environment which there is a taxation level of 23% (one of the highest in the world). In Portugal, for instance, the tax on medicine is 4.7%) and a price control policy that suffocates the companies and inhibits the sector's development.

Each year, more and more national and international laboratories try hard to discover and synthesize new active substances, taking advantage, among other factors, of the Brazilian biodiversity.

The Center of Biotechnology of Amazonia (CBA) invested R$14 million to build a complex of 12,000 square meters, which is situated in the area of the industrial state of Manaus, and will have the units of basic and advanced research of cosmetic companies, phytotherapeutic agents, and extracts that

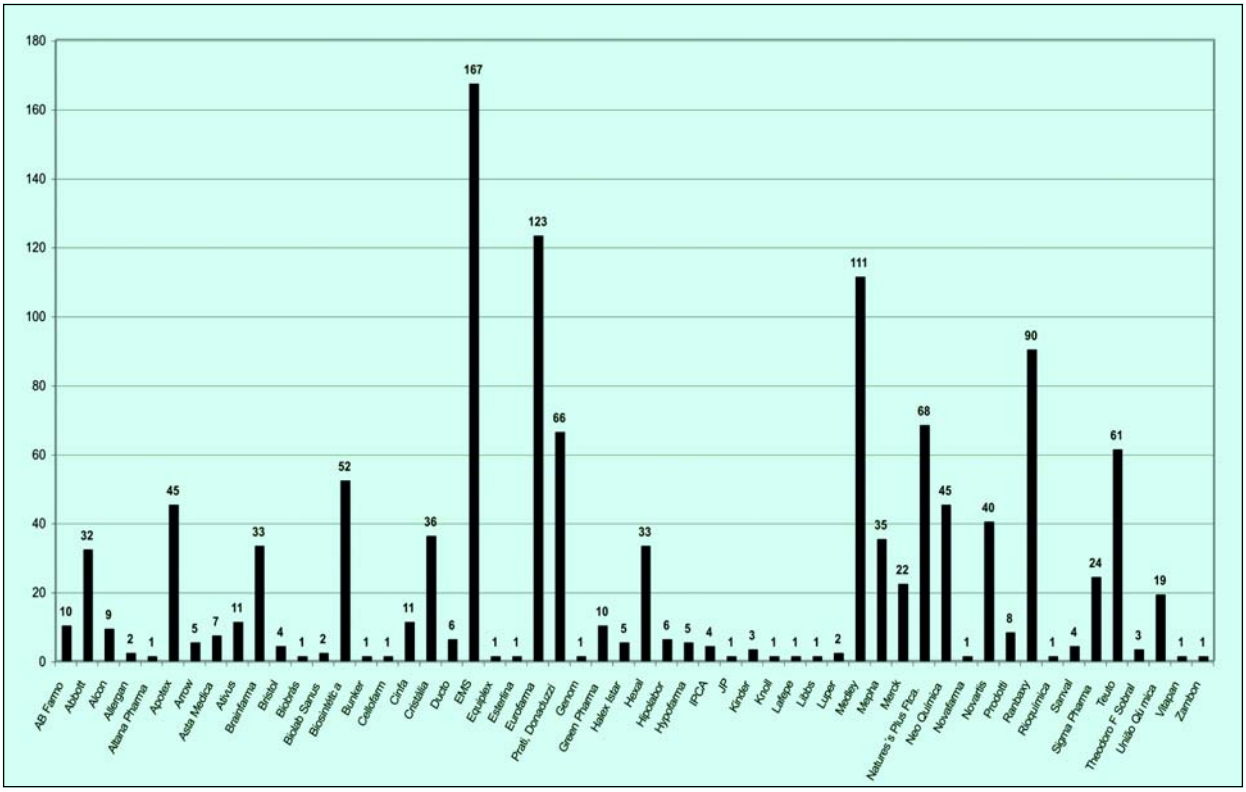


Figure 1. Total of registered generic drugs by company.

use the raw material from the Amazonica region, the planet's highest concentration of biodiversity. CBA was built using mainly the resources of the Zona Franca de Manaus Superintendency [Suframa that today is under the Ministry of Development, Industry, and Foreign Trade (MDIC) and Science and Technology (MCT) and Environment (MMA).]

According to the CBA technical assessor, Imar Cézar de Araújo, by the end of 2004, the first 11 laboratories (from the total of 26) will be operational. Araújo explains that the programs to be developed represent in the medium and long run, the possibility of multiple opportunities of investments necessary to the installation of a bioindustry park which will attract new companies, enterprises, and businesses. To enable this, according to the coordinator, it is necessary to have qualified workers, opening new opportunities to researchers of the region and of the country.

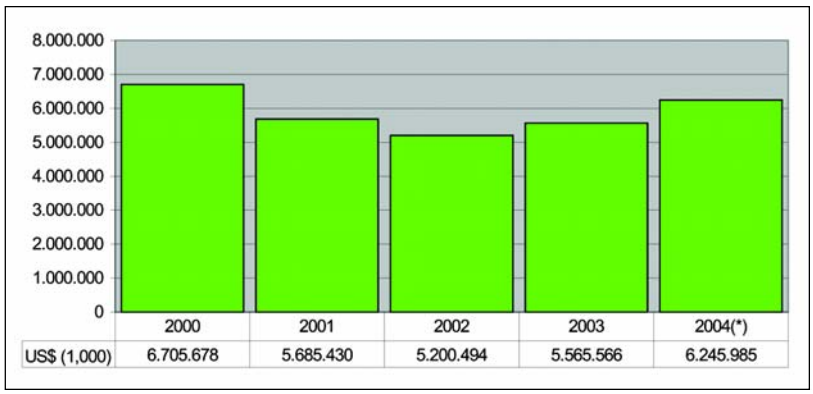
The center also will stimulate the areas of science, technology, and technological innovation to increase competition of the so-called bioproducts, and of the farming products produced in the Amazonas region. Among the activities, there are the certification of the natural products from Amazonas, having a quality assurance stamp (CBA stamp) and the transfer of the technology of processes and patents developed at the center and at the Rede de Laboratórios Associados - Net Associated Laboratories (RLA). The net will link universities and public and private research centers, such as Instituto Nacional de Pesquisas da Amazônia, Museu Emílio Goeldi and Federal Universities of Amazonas and Pará and also Fundação Fiocruz and Oswaldo Cruz among others.

The CBA was created in the scope of Brazilian Program of Molecular Ecology for the Supported Use of Amazonas Biodiversity (Probme/Amazônia), and this year, it has been included in the government industrial, technological, and international trade policy. According to the technical assessor, the center will have a laboratory complex of international standard aiming the applied research, technology transfers, and rendering services of a high level. When those projects are implemented, CBA will act in bioprospection identifying and extracting the active ingredients from plants and animals to pharmaceutical use, as for example, antibiotics, anti-neoplastics, anti-hypertensive substances, and different products as vegetal raw material to make biocosmetics, natural colorants, aromatic substances, essential oil, biodegradable polymers, bio-insecticides among others. In the section of phytotherapeutic, phyto-cosmetics, and fruit culture, CBA was projected to also attract new business and new companies strengthening the productive chain with the consequent settlement of small producers.

A View of the Brazilian Pharmaceutical Industry

Continued from page 3.

ported the equivalent of $279.9 million. In the first six months of 2004, Brazilian pharmaceutical companies have exported $163.9 million in finished medicine and similar products, vaccine, serum, blood derived products, and parenteral solutions, a growth of 17.85% in relation to the same period last year. The exportations to Mercosur increased 14.77% in the first quarter comparing to the same period last year, and the result was $43.6 million. The most important import markets last year were Mercosur; Argentina, Mexico, and Venezuela.[2]



	2000	2001	2002	2003	2004(*)
US$ (1,000)	6.705.678	5.685.430	5.200.494	5.565.566	6.245.985

Figure 3. Brazilian pharmaceutical market in USD$ (1,000).[1]

Prescription drugs as well as Over the Counter (OTC) products are primarily distributed through drugstores/pharmacies, clinics and hospitals.

In the retail, there are 55,000 points of sale (drugstores/pharmacies) in Brazil, with an average of 23% of the products that are not medicine (cosmetics, hygiene, etc.) and 77% of medicine.[2]

The demand of the products is mainly originated by the doctors' prescriptions, in which the industries invest 80% to 85% of the marketing amount. Using the

Concludes on page 7.

Brazilian Pharmaceutical Market

by Antônio Costa, ex. Altana Pharma Market Research and GRUPEMEF (Pharmaceutical Market Researcher Group) and Sérgio Mena Barreto, ABRAFARMA President

In Brazil, there are some class associations that represent the pharmacies such as the Brazilian Association of Pharmacies (ABRAFARMA), the Brazilian Association of Pharmaceutical Trade (ABCFARMA), among others. Both associations represent a total of 90% of the retail pharmaceutical market.

ABRAFARMA was founded to be representative and to be trusted by the government in negotiations of the sector.

ABRAFARMA is the reunion of 28 companies with the biggest drugstores in Brazil having 1,800 stores. The association represents around 27% of the medicine in Brazilian market and involves R$5.6 billion per year. 25% of the sales are of non-medicine products. Founded in 1991, it has companies in 237 cities in 19 Brazilian states that employ 33,284 people. It focuses on the improvement of the associated companies to preserve the institutional image, the relationship with public institutions, government and suppliers, and also the legal support and market research to improve the activities.

In Brazil today, the drugstores survive due to the sales of products that aren't medicine. In a traditional drugstore, 75% of the sales are of drugs, 25% are shampoos, diapers, hair color, blood glucose monitoring systems, vitamins among others. The small stores have low billing and high informal level with a monthly income between R$ 30,000 and R$ 40,000. (Source: ABRAFARMA)

The research also has shown an increase of 12.21% in the number of product units sold and the delivery system already represents 3.61% of the sales.

In Brazil, there are 53,000 drugstores, 80% of them are small stores with low billing and high informally level with monthly income between R$30,000 and R$ 40,000.

The initial investment to open a drugstore is low. It is possible to buy a drugstore for R$ 50,000,00 or R$ 70,000,00. Drugstores in Brazil earn their profit primarily through the sale of non-medicine products. Abrafarma final net profit is around 1.5%. The data have been audited by Fundação Instituto de Administração (Fia). This result is generated by the non-medicine products. The organization completely supports the initiative of the President Luiz Inácio Lula da Silva in reducing the State VAT (ICMS) of the medicines in Brazil. If he manages to do that, the Federal Government will solve the problem of inequity that has been happening with millions of Brazilians: the huge amount of taxes that the patient has to pay on drugs.

In Brazil, the State VAT on medicine is between 17% and 19%. Those high taxes increase the price of the drugs to the final consumer; burden the companies that pay more. ABRAFARMA has been trying to negotiate with the government a tax reduction to 7%. Today, the level of taxes is 18%.

The solution to provide medicine for a country with 180 million people is to offer individuals the generic drugs; the government provides medicine to the population that can afford a treatment that is 40% cheaper. And the popular drugstore was started to help those people whose income is between two and three minimum wages and can afford very little. But there is a big part of the population that the solution is the distribution of free medicine performed by Sistema Único de Saúde = Unique Health System (SUS) maintained by the government.

At the popular drugstore, people can find 86 drugs at low prices. Doctors prescribe 10 thousand drugs in Brazil. At the popular drugstore, 70% of the products are of public production. So, out of the 86 drugs prescribed, 77 are of public production and the other 19, bought from private industries. They are products of good quality.

The number of jobs in drugstores is increasing because it is easy to open a drugstore, as long as you have an appropriate location and abide by government regulations. The City Hall requests a permission to work, controls, and registers a pharmacist. There are no obstacles. A medium-size drugstore can employ an average of 14 people in each store.

This is a situation that will change in a few years with the number of new colleges that have been opened lately; we should get to the year 2005 with a considerable number of graduated professionals. In Brazil, 14 thousand pharmacists graduate every year.

In charge of Abrafarma for the third time, Sérgio Mena Barreto fights for the regulation of many drugstores spread all over Brazil. He defends the reduction of the tax rate on medicine as well as government actions to allow the population access to medicine as in the use of generic drugs and the popular drugstore.

Professional Profile

by Renato Pimazzoni, President, Formil Pharmaceutical

The level of education required in the pharmaceutical industry is high because individuals are responsible for industrial, administrative, and commercial areas.

The professional working in the industrial arena must be graduated in chemist-pharmacy, industrial chemistry, engineering, and must have vast experience in the pharmaceutical sector.

The industrial area demands highly trained professionals in the production, products development, and quality control sectors.

Research and development in the Brazilian pharmaceutical industry is performed by a few companies that invest in new drugs research; one of the projects that has received attention from the government and from the largest Brazilian pharmaceutical laboratory (Laboratórios Aché) that includes phytoterapeutic agents due to the diversity of Brazilian flora.

Another professional of great importance is the one responsible for regulatory issues whose task is to register the products at the government Agência Nacional de Vigilância Sanitária (ANVISA).

The marketing of Brazilian pharmaceuticals is regulated by ANVISA and prohibits direct to consumer advertising. All technical information is exclusive to the doctor; therefore, the medical advertisement is the most important tool to advertise the product.

The Brazilian market has 140,000 doctors, of which 40% are in south and southeast regions which correspond to 60% of the prescriptions.

In a highly competitive market, the necessity to narrow the relationships with doctors and drugstores are the companies' basic strategies.

Thus, the company's marketing must be synchronized with the market and with its sales force, whereas the latter is the means of communication with the clients and also the information source about market acceptance and the competitors' actions.

The pharmaceutical industries professional representatives are highly trained, receiving instructions about pathologies and therapy as well as continuously updated market information. Today, 80% of the sales force has university degrees.

In addition to the distribution of medical advertisement, the professional representative visits the drugstores in order to obtain information about the company's product line, it's not a sales visit because the sales are performed by the suppliers/wholesalers.

To increase the visits to the doctors in some specialties, some companies hire a group of trainees (directly or through companies specialized in training and forming groups of representatives). PE

A View of the Brazilian Pharmaceutical Industry

Continued from page 5.

media for OTC products, the investment is still too low, because most of the population still follows the advice of the drugstore professional.

The Brazilian pharmaceutical market shows a growth potential, mainly in drugs of continuous use, because the population of elderly is increasing while the birthrate is going down.

In Brazil, there is no medicine reimbursement system, therefore, the acquisition of a product is totally paid by the user, or it may be received free of charge through a governmental health organ, in the latter the patients must be enrolled in the organ.

The official government laboratories still don't have high productive capability and they produce some products for their own use in their hospitals, and these products cannot meet the necessity so the products are not sold in the selling points.

In the last five years, the national companies have intensified the partnerships with multinational companies, producing and selling their products, having as a result the investment in the modernization and automation of the industrial plants, and in many of them, including the ones belonging to the big international corporations.

The Brazilian pharmaceutical industries have today a modern industrial estate that meets all the international demands in quality control, and production capacity to internal and external market.

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Brazilian Associations and Agencies

Brazilian Regulatory Agency

Agência Nacional de Vigilância Sanatária (ANVISA)

End.: SEPN 515, Bl B - Edifício Ômega
Brasilia - DF
Cep: 70.770-502
Brazil
www.anvisa.org.br

Brazilian Pharmaceutical Associations

Federação Brasileira da Indústria Farmacêutica (FEBRAFARMA)

Rua Alvorada, 1280 - Vila Olímpia
São Paulo / SP
Cep: 04550-004
Brazil
Tel: 55-11-3046-9292
www.febrafarma.org.br

Associação Brasileira da Indústria de Medicamentos Isentos de Prescrição (ABIMIP)

(OTC´s Brazilian Industry Association)
Rua Alvorada, 1280 - Vila Olímpia
São Paulo / SP
Cep: 04550-004
Brazil
Tel: 55-11-3045-3842
www.abimip.org.br

Associção dos Laboratórios Farmacêuticos Nacionais (ALANAC)

Rua Sansão Alves dos Santos, 433 - 8º. andar - Brooklin Paulista
São Paulo / SP
Cep: 04571-090
Brazil
Tel: 55-11-5506-8522
www.alanac.org.br

Associação de Indústria Farmacêutica de Pesquisa (INTERFARMA)

Rua Fernandes Moreira, 1166 - cjto. 72 - Santo Amaro
São Paulo / SP
Cep: 04716-003
Brazil
Tel: 55-11-5180-2380
Fax: 55-11-5183-4247
www.interfarma.org.br

Associação Brasileira de Medicamentos Genéricos (PRÓ-GENÉRICOS)

Rua Alvorada, 1280 - Vila Olímpia
São Paulo / SP
Cep: 04550-004
Brazil
Tel: 55-11-3897-9767
Fax: 55-11-3845-0742
www.progenericos.org.br

Associação Brasileira de Redes de Farmácias e Drogarias (ABRAFARMA)

Brazilian Pharmacy Association
www.abrafarma.com.br

Brazilian Entities

Associação Brasileira das Indústrias de Química Fina, Biotecnologia e suas Especialidades (ABIFINA)

http://www.abifina.org.br

Associação Brasileira da Indústria Farmoquímica (ABIQUIF)

http://www.abiquif.org.br

Associação Nacional de Farmacêuticos Magistrais (Anfarmag)

http://www.anfarmag.com.br

Grupo dos Profissionais Executivos do Mercado Farmacêutico (GRUPEMEF)

http://www.grupemef.com.br

Sociedade Brasileira de Vigilância de Medicamentos (Sobravime)

http://www.sobravime.org.br