While the global pharmaceutical industry tends to be conservative in nature, its implementation of newer technologies for aseptic processing has been impressive—and nowhere more so than in Japan. Shibuya Kogyo (Kanazawa, Japan), in conjunction with La Calhene (Vendôme Cedex, France), introduced isolators for aseptic manufacturing to the Japanese market in 1994.

Over the last dozen years, more than 40 isolator-based production lines have been installed and validated throughout the country.

Isolators are used in a wide variety of applications, including both large- and small-volume parenterals, lyophilized products, powder fills, combination products, medical devices as well as more typical liquid fills into a single container. In addition to advanced aseptic processing environments such as isolators, Japanese firms have been more aggressive than some of their international counterparts in the adoption of factory automation and robotics.

Japan has also been very active over the same period of time in developing its regulatory guidance. In 2005, a task force comprised of industry, academic and government experts released “Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing” (Box, p. 26). This comprehensive 99-page document covers all aspects of aseptic processing including production facilities, utility systems, sterilization equipment and environmental management, process simulation and control. Additionally, it provides information pertinent to design and validation of advanced technologies such as isolators and blow/fill/seal.

Japanese standards regarding aseptic processing, notably those for environmental monitoring recommendations, media fill procedure/acceptance criteria and validation approaches, are all compatible with those of FDA and EMEA. This is not surprising since all three regulatory bodies are members of the International Congress on Harmonization (ICH).

However, relatively little information is available in Europe and North America regarding aseptic processing requirements and facilities in Japan. This article will shed some light on Japanese aseptic practices and Japanese innovation in aseptic processing.

**HOW JAPAN IS DIFFERENT**

Japan, like the other constituents of the ICH, has its own well-developed pharmaceutical manufacturing equipment industry, and is capable of supplying all of the equipment and facility infrastructure required for a modern aseptic processing facility. The country has also developed considerable capabilities in electronics, robotics, optics and in-process analysis. Japanese requirements for computer system validation have been pragmatic and objective, and have not prevented pharmaceutical manufacturers from using advanced process control technologies, robotics and machine automation.
Some of the noteworthy aspects of aseptic processing in Japan include:

• Automation of component supply feeding systems to reduce repetitive work and contamination risk. The use of automatically guided vehicles for logistics support, process line automation and automatic loading and unloading of lyophilizers is very common in new facilities.

• A high level of direct process monitoring for many production parameters such as throughput, fill volumes and component feed status. Japan has not had to deal with some of the circumstances related to 21 CFR Part 11 regarding validation of computerized process or information technology systems.

• Near paperless manufacturing, with detailed operating instructions and all key inputs available on touch screens.

• Extremely high levels of process performance in terms of throughput, efficiency and reliability in all aspects of the manufacturing process.

• The common use of video systems to enable direct visual monitoring of aseptic area operations. In addition, advanced facilities monitoring systems are provided in a central control room. These systems are capable of measuring all key environmental parameters, including airborne particle levels.

A CASE IN POINT: HANDAI BIKEN

The following case study serves as an excellent example of a modern Japanese aseptic processing facility. This aseptic processing manufacturing line is installed at the Handai Biken facility in Kagawa, Japan, and is dedicated to the aseptic bottling of vaccines in vials. The Kagawa facility was built and the equipment installed in 2004, and commercial production of vaccines commenced in 2005. The facility can produce lyophilized and liquid-filled vials.

All product filling, lyophilization and stoppering at the site are conducted in vertical unidirectional airflow isolators, which are designed and operated to comply with ISO 14644 Class 5 requirements. The environment surrounding the isolators complies with ISO Class 7 requirements. Handai Biken developed user requirement specifications (URS) for this project, in order to minimize the risk of contaminating the biological products. The production systems are designed to minimize particulate contamination as well as human intervention. Additionally, a number of design features were implemented to ensure high yields and minimal line stoppages.

ISOLATORS

The project consists of five isolator sections:

1. Between the tunnel and filler (3.9 m³ total enclosed volume)
2. Filling/stoppering machine (4.8 m³)
3. Rubber stopper supply system (16.9 m³)
4. Lyophilizer conveyor (3.9 m³)
5. Automatic lyophilizer loading/unloading (17.0 m³)

The total enclosed isolator volume for these five sections is 47.4 m³. To facilitate vapor hydrogen peroxide decontamination, the isolators are divided into two sections. The first section, which consists of the isolators described in items 1-4 above, has a total enclosed volume of 30.4 m³, while the second decontamination group consists only of the fifth isolator.

Decontamination is accomplished by VHPM1000S vapor phase hydrogen peroxide generators sourced from Steris Corp. (Mentor, Ohio). The isolator network is divided into two sections for decontamination, in order to ensure that the total volume and surface area to be treated is within the capacity of the vapor phase hydrogen peroxide generators.

The isolators are equipped with dehumidification units to reach the relatively low humidity levels required by the Steris vapor phase hydrogen peroxide generators prior to the decontamination process. Decontamination of the isolators was validated using G. stearothermophilus biological indicators on stainless steel coupons with a population of 106 spores per indicator. The acceptance criterion for decontamination was complete kill of all biological indicators placed within the isolators.

Following are functional descriptions of each major piece of process equipment on the line:

Vial washer: The vial washer uses hot water for injection and, in typical washer designs, this results in the formation of water vapor under the top cover of the machine. Handai Biken engineers were concerned about the negative air pressure
VITAL PRODUCTION STATISTICS AT HANDAI Biken

The following are critical production statistics for the aseptic vaccine filling line at Handai Biken:

1. Filling speeds: 400 vials/minute for 2-mL vials and 200 vials/minute for 7-mL vials. In the future, the system will be equipped to handle 10-mL vials.
2. Container type: Glass vials, 2 mL and 7 mL.
3. Stopper types: Five types of rubber stoppers are used: lyophilization stoppers for both 2-mL and 7-mL vials, and three different types of conventional stoppers for 2-mL vials.
4. Aluminum caps: Two types, one for 2-mL containers and another for 7-mL containers.
5. Product types filled: a clear vaccine solution with a mean viscosity of 2 cp., and a vaccine suspension, which will sediment without mixing.

that would develop within the top cover. With Shibuya, they developed a double-shell washer system, in which positive HEPA-filtered air is supplied between the outer and inner shells of the machine cover to preclude the entrainment of particulate matter from the surrounding environment. This ensures that the vials are washed and handled in a clean, high particulate air quality environment.

Dry heat tunnel and interface isolator: The dry heat tunnel is equipped with a fully dry-heat-sterilizable cooling zone, which can be sterilized by dry heat at 170°C for 20 minutes during changeover periods. This sterilization process is fully validated. A vial counting system is used in front of the inlet to form a single row and ensure the smooth feeding of glass with minimum pressure on the glass pack. Rows are fed intermittently to ensure that no horizontal pressure is applied to vials already moving on the conveyor. Thus, minimum horizontal pressure is required to feed each row of vials onto the conveyor, which eliminates “crashing” of glass and prevents particulate formation, or vial breakage resulting from hard glass-to-glass contact.

Aseptic filling machine/rubber stopping machine and isolator: Fill mass (volume) is controlled by means of eight mass flow meters, each of which supplies a single fill point or needle. All filling data are digitized and stored electronically. This enables the system to record the precise fill data including mass, vial number and time and to display this data on the control panel. A full summary of all filling data for each filled unit can be printed out on a daily basis. All product contact parts within the mass flow meters are composed of 316L stainless steel. The mass flow meters can be fully cleaned and sterilized in place.

Handai Biken engineers specified that, in addition to the mass flow metering system, fill weights must also be taken gravimetrically. Eight load cells can perform the fill-weight function in approximately ten seconds. The gravimetric weight check system was originally used at 15-minute intervals throughout the filling operation. Because the flow-metering system proved to be extremely accurate and reliable, the engineers decided that it was not necessary to check fill volumes gravimetrically throughout the filling process. Actual mass flow fill accuracies have been +/- 0.5%, which is well within the +/- 1% validation acceptance criterion. Therefore, fill volumes are now checked by the load cells only for reference purposes during set-up.

The fill machine’s cantilever construction allows for all maintenance to be performed from outside the isolator enclosure. Also, there is no equipment located under the filling needles, which allows air to flow undisturbed to the air returns on the floor of the machine. This design ensures undisturbed unidirectional airflow through the critical aseptic zone.

Rubber stopper supply system: The rubber stopper supply system is one of the most important design features...
ASEPTIC PROCESSING GUIDELINES IN JAPAN

The following are basic elements of Japan’s “Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing.”

- **Personnel**: The guideline clearly states that human operators are the greatest source of contamination in aseptic processing and defines a comprehensive set of goals and objectives in personnel training. These include expertise in aseptic techniques and a working knowledge of microbiology, including specific knowledge “regarding species likely to be encountered.” Additionally, personnel are to be comprehensively trained regarding gowned and evaluated regarding their gowned ability. Finally, workers are expected to have a working knowledge of the principles of cleaning and disinfection.

- **Quality systems expectations** are defined in the Guideline, including systems for document control, organizational structure, risk analysis and qualification of equipment and processes.

- **Requirements for facility design and room classification** are set forth in detail. Critical areas are required to meet Grade A expectations for both total particulate and microbiological contamination. Support areas are to comply with Grade B requirements. The conditions stipulated for design, management and control of aseptic processing environments very much parallel those of the EU GMPs. Pressure differentials of 10-15 Pa are required between adjacent rooms of different classifications so that a proper air pressure cascade can be established and maintained.

- **Disinfectants and sanitizing agents** must be validated to be free of microbial contamination at the time of use, and the methods for their application must be verified/validated for effectiveness. Tests should also be conducted to ensure that residues can be reduced to a pre-defined level.

- **Component washing** must be validated to remove at least 99.9% (3-log reduction) of bacterial endotoxin.

- **Environmental monitoring in Grade A critical zones** for airborne contamination is to be done for each shift of operation. Operators are also to be sampled for microbial contamination once per shift. Surface monitoring is to be done at the end of each production operation. Particulate monitoring is to be done “throughout the entire aseptic procedure” in all Grade A environments.

- **All product contact materials** including container/closure systems and sample filters must be sterilized according to a validated process. The efficacy of the sterilization process must be verified using biological indicators. Specific guidance is provided on all sterilization methods used in industry. A separate section is dedicated to directions for the use of Sterilization-in-Place systems.

- **The Guideline suggests that isolator-equipped operations should keep “the number of half suits, gloves, transfer ports, and connections … to a minimum in order to reduce the chance of contamination.”** Isolators are also required to have a minimum positive pressure differential of 17.5 Pa relative to the surrounding environment, which is expected to meet Grade D requirements.

- **Media fills** must comprehensively challenge the entire process, including all product-contact equipment, and must consist of 5,000 units as a general recommendation. All shifts must participate in media fill tests and all interventions must be included in each test. Media fills should cover the longest production time utilized in actual production.

of this entire processing system. Handai Biken and Shibuya Kogyo recognized that one of the most frequent interventions required in aseptic vial processing lines is to stage rubber stoppers and manually place them into the stopper feed hopper. In a filling system capable of line speeds of up to 400 vials per minute, stopper supply can be labor intensive, and batch processing of stoppers would require significant storage space after autoclaving. It was also determined that, at the stopper consumption rate required for this filling system, the use of a rapid transfer port or “Beta-Bag” system might not be practical.

To resolve these issues, Shibuya provided a stopper washing system that washes each stopper individually to ensure gentle handling and minimal particulate generation. The stopper washing system automatically feeds the stoppers into custom-designed stainless steel stopper cans, which are perforated for good steam penetration during autoclaving. These cans are fed automatically into a dedicated autoclave in which all stoppers are sterilized using a validated moist heat process.

After the cycle is complete, the autoclave is automatically unloaded using robotics, and the sterile stopper-filled cans are accumulated within a conveyor inside the stopper supply isolator. Robots lift the cans and tip the stoppers into the hoppers as required. Empty cans are returned to the autoclave, which serves as a pass box for transfer of these empty cans back to the loading side of the autoclave, where they are prepared for their next use.

This automatic stopper preparation and feed system offers a tremendous advantage over more conventional manual systems. The combination of automation and robotics eliminates the potential ergonomic problems of conventional isolators and minimizes contamination risk by avoiding the use of gloved interventions. And, since no autoclave bags or wraps are required for the operation, the approach eliminates a great deal of waste that would normally have to be removed from the isolator. This system has proven to be efficient
and extremely reliable in day-to-day production operations.

The implementation of the stopper supply system also required robots capable of withstanding vapor phase hydrogen peroxide decontamination. These robots do not contribute to particulate contamination, which would be considered significant in an ISO Class 5 environment. In fact, studies have determined that they would be suitable for use in an ISO Class 4 environment.

These robots were co-developed by Shibuya Kogyo Co., Ltd. and Fanuc Robotics (Rochester Hills, Mich.) specifically for use in aseptic processing environments where resistance to cleaning and disinfection agents as well as low particulate generation are very important.

**Lyophilization/aluminum cap sealing:**
Half-stoppered vials are conveyed from the stoppering unit to the lyophilizer all within isolators. All loading and unloading of the lyophilizer is fully automated and requires no operator intervention. The fully stoppered vials, once unloaded, are conveyed to an aluminum cap applying and sealing station. This station is located within a unidirectional HEPA-filtered clean booth that meets ISO 5 conditions.

**Environmental monitoring systems:**
Environmental microbiological air sampling systems are located within the isolator network and sites, and were carefully considered during the design process. The air sampling units are fully decontaminated with vapor phase hydrogen peroxide to minimize the possibility of false-positive results. HEPA filters mounted at the distal end of the supply system, external to the isolator, protect against contamination from the surrounding environment affecting the isolator environment. Microbial sampling can be accomplished easily, and with minimal risk of contamination in sample taking or handling. Additionally, the filling system is equipped with automatic electronic particulate air sampling devices.

The isolator-based aseptic filling line described in this article was conceived and built in Japan using equipment sourced nearly exclusively from Japanese vendors. We believe the filling system described here is fully state-of-the-art and will meet all global production quality and validation requirements.

An important trend in aseptic manufacturing will be the elimination of human contamination and ease of operation in separative environments such as isolators. The use of carefully designed automation and robotics can both reduce contamination risk by eliminating many interventions and also improve productivity and reliability.

We can envision a future in which the need for human operators for direct intervention in aseptic operations will be eliminated.

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