United States (U.S.) pharmaceutical corporations are major worldwide manufacturers of various drug dosage forms. Although many are headquartered in the U.S., most have research and manufacturing facilities located throughout the world. These research facilities are utilized for chemical development and produce raw materials for clinical supplies used on a global basis. Their manufacturing plants are usually designed in accordance with Current Good Manufacturing Practices (cGMPs), as addressed in the U.S. Code of Federal Regulations (CFR) Title 21 Parts 210 and 211. Since these facilities produce solid dosage forms for global distribution, they must incorporate the design, construction, and validation requirements of international regulatory bodies in Europe, the Pacific Rim, and the U.S.

Adherence to GMPs, when engineering pharmaceutical manufacturing facilities, is a requirement of regulatory bodies throughout the world. Failure to abide by the regulatory requirements means that a facility is non-compliant and will not be approved for operation. This can result in significant financial loss. Thus, it is in the best interest of global pharmaceutical manufacturers to assure that all new facilities are designed in accordance with local regulations where they intend to market their drug products.

Regulatory bodies such as the U.S. Food and Drug Administration (FDA), the Commission of the European Communities, and the Japanese Ministry of Health and Welfare (MHW) have recently taken great strides towards harmonization. In fact, Section 40 of the Food and Drug Modernization Act of 1997 mandates the “pursuance of international cooperative agreements to reduce the burden of regulation and harmonize regulatory requirements if consistent with consumer protection requirements of the Food, Drug and Cosmetic Act.” Toward this end, the U.S. and the European Union (EU) have entered into a Mutual Recognition Agreement (MRA). The MRA establishes the following principle: A manufacturer is in regulatory compliance in Europe and/or the U.S. should either party find the manufacturer in compliance with their own estab-
lished conformity assessments. Japan, Europe, the U.S., and other Pacific Rim nations convened the International Conference of Harmonization (ICH) in 1989. The purpose of this conference was to establish an expert working group whose responsibility it is to develop a GMP document that combines the existing guides and draft guides from the various regulatory bodies into a single document that will be accepted worldwide. Included in this guide will be sections on buildings, facilities, and process equipment. The draft for this document is scheduled for public comment sometime this year.

Though the worldwide pharmaceutical community is approaching harmonization it is not yet at this stage. As a result, it is still necessary for pharmaceutical companies to adhere to various worldwide regulatory requirements. A close examination of the regulations shows that there are many similarities. There are also differences through which companies must be cognizant of if they expect to sell their products globally. Even with the MRA in place between the U.S. and Europe, there are still equivalency issues such as manufacturing standards, inspection requirements, and enforcement authority. It can also be expected that there are differences in design requirements that must be addressed.

A facility is defined as a production building housed within a defined boundary. Within the facility, designed to support the various manufacturing and support systems, are the utilities. Together, these systems support the equipment used in various processes to manufacture finished solid dosage forms. The focus of this paper is on the requirements for manufacturing solid dosage form drugs. This paper will compare and contrast published regulations from the U.S., the EU, and Japan as related to various engineering aspects of solid dosage form facilities. It will identify where major differences may occur in requirements for material and personnel flow, Heating, Ventilation, and Air-conditioning (HVAC) and containment, fire and safety, waste disposal, cleaning and maintenance of manufacturing and non-manufacturing areas, and general facility utilities.

The cGMP regulations under 21 CFR, Parts 210 and 211, apply to finished dosage form drugs. Section 501 (a) (2) (b) of the Food, Drug, and Cosmetic (FD&C) Act requires that all drugs be manufactured, processed, packaged, and warehoused in accordance with cGMP.

Solid Dosage Form Facility

Solid dosage form drugs include tablets, capsules, and suppositories intended for the diagnosis, treatment, mitigation, and cure of disease conditions in humans or animals. Measurable quantities of solid dosage forms are manufactured as a batch process. Within each batch there are discrete unit operations, that when combined into a logical sequence, result in the finished dosage form. It is common practice for a solid dosage form facility to be used for the manufacture of multiple, non-related products. Separation of products from the initial unit operation of weighing through final compression, encapsulation, or molding is required by regulation.

Solid dosage form facilities in the U.S. must comply with FDA cGMP guidelines and various sections of the CFR. Where U.S. manufactured products are to be sold in either Europe or Japan, the conditions of manufacture must also meet these nations’ requirements as well.

Process Flow of Materials and Personnel

- The U.S. GMPs state that “the flow of materials shall be designed to prevent contamination,” Sec.211.42 (b).
- The EU GMP further mentions that “the adequacy of the working and in-process storage space should permit the orderly and logical positioning of equipment and materials so as to minimize the risk of confusion between different medicinal products or their components; to avoid cross-contamination and to minimize the risk of omission or wrong application of any of the manufacturing or control steps,” EU-3.8.
- The translated Japanese GMP mentions that, “The facilities for a drug manufacturing plant shall have adequate facilities for the sanitary and safe storage of raw materials, labeling and packaging materials, and products,” Ordinance No. 29Art5.

It is recognized that personnel are integral to manufacturing, but only those trained and required should have access to the various unit operations being performed.

- U.S. GMPs state that “only personnel authorized by supervisory personnel shall enter those areas of the building and facilities designated as limited-access areas,” Sec. 211.28(c).
The EU GMP mentions that, “Steps should be taken in order to prevent the entry of unauthorized people. Additionally, production, storage, and quality control areas should not be used as a right of way by personnel who do not work in them,” EU-3.5.

The Japanese GMP states that “the work-room shall be constructed so as not to allow passage for personnel other than those working in the room. Note: This provision shall not apply when there is no risk of contamination by personnel other than those working in the room;” Ordinance No. 29, Art. 5, Par. 3, Item B.

HVAC and Containment

Solid dosage form facilities must contain ventilation suitable to support manufacturing personnel, while designed to prevent cross-contamination between products being manufactured in various locations within the facility. There are several methods to accomplish this objective. One way is to use ventilation systems dedicated to specific areas constructed with floor-to-ceiling partitions, and containing airlocks for separation. These areas could be designated as either classified or non-classified areas with respect to the number and size of particles per cubic foot or cubic meter. Another way is to employ dedicated ventilation systems for totally enclosed workstations. This includes glove boxes and containment booths. Another alternative is to employ pressure differentials between areas designed to prevent cross-contamination.

The U.S. GMPs state that, “Air filtration systems shall be used when appropriate on air supplies to production areas. If air is recirculated to other production areas, measures shall be taken to control recirculation of dust from production. In areas where air contamination occurs from production, there shall be adequate exhaust systems;” Sec. 211.46(c).

The EU GMP specifically mentions dust. “In cases where dust is generated, specific provisions should be taken to avoid cross-contamination and facilitate cleaning,” EU-3.14.

The Japanese GMP specifically covers dust, microorganisms, and the potential for worker anaphylaxis from inhaled material. “The work-room shall be provided with facilities and equipment for the prevention of contamination by dust and microorganisms, depending on the type, dosage form, and manufacturing process of intended drug. Provision: This shall not apply when the same effects are obtained from the functions of the manufacturing facilities. When a drug which is easy to disperse and cause anaphylaxis in small quantities or a drug which has serious effects on other drugs by cross-contamination is manufactured simultaneously with other drugs, the work room and air handling system shall be separated from those used for other drugs;” No. 29, Art. 5-2, Par. 3, Items H, I.

Humidity and dehumidification of ventilated areas are used for both worker health and safety (Occupational Safety and Health Administration [OSHA], National Institute of Occupational Safety and Health [NIOSH]), and to meet environmental limitations to insure material and product stability. HVAC systems in the U.S. usually incorporate humidity and dehumidification equipment as part of their air-handling units.

The U.S. GMPs state that, “Equipment for adequate control over air pressure, microorganisms, dust, humidity, and temperature shall be provided when appropriate for the manufacture, processing, packing, or holding of a drug product;” Sec. 211.46(b).

The EU GMP states that, “Production areas should be effectively ventilated, with air control facilities (including temperature and, where necessary, humidity and filtration) appropriate both to the products handled, to the operations undertaken within them and to the external environment,” EU 3.12.

No mention is made in the Japanese GMP regarding control over temperature and humidity.

Classified areas with respect to the number and size of particles per square foot or square meter are designed to protect the unpacked product from the environment. They range from walk-in suites through air locks to glove boxes, or isolators, to fume hoods. For non-sterile pharmaceutical manufacturing areas in the U.S., the usual classifications are: unclassified, Class 100K, Class 10K, and Class 1000. Figure 1 compares the particulate requirements for classified areas for the U.S., EU, and Japanese regulations. Note that the International Organization of
The U.S. GMPs state that, “Air is generally of acceptable particulate quality if it has a per cubic foot particle count of not more than 100,000 in a size range of 0.5 micron or larger (Class 100,000).” For unclassified areas, only the U.S. GMPs list recommendations: “A minimum of 30% ASHRAE [American Society of Heating, Refrigerating, and Air-Conditioning Engineers] filtration is recommended.”

No specific mention is found in the EU GMP regarding classified or unclassified areas.

Similarly, no specific mention is found in the Japanese GMP for classified or unclassified areas.

Airlocks and separation of the workplace, where solid dosage forms are manufactured and packaged, are designed to prevent airborne contamination and physical mix-ups, respectively. These areas are addressed by both the U.S. and EU GMPs. They are not specifically mentioned in the Japanese GMP.

The U.S. GMPs state that, “Operations shall be performed within specifically defined areas of adequate size. There shall be separate or defined areas or such other control systems for the firm’s operations as are necessary to prevent contamination or mix-ups...” Sec. 211.42(c).

The EU GMP addresses this topic saying, “Cross-contamination should be avoided by appropriate technical or organizational measures. For example (a) production in segregated areas or by campaign (b) providing appropriate airlocks and air extraction (c) minimizing the risk of contamination caused by recirculation or reentry of untreated or insufficiently treated air,” EU 5.19.

Fire and Safety
Although not specifically mentioned in the GMP of all three regions, in the U.S., compliance with the National Fire Protection Association (NFPA) or equivalent code is considered by the authorities that issue Certificates of Occupancy.

According to the International Society for Pharmaceutical Engineering (ISPE) Baseline Guide for Oral Solid Dosage form facilities, design considerations include:

- The need for pressurization of exits and stairwells whenever emergency ventilation or a fire alarm is actuated
- Smoke purge and control systems
- Impact of fire damper placement on emergency ventilation and smoke control
- Air system operation in the event of a hazardous spill

Waste Disposal
Globally, the proper disposal of various classes of waste has led to the promulgation and enforcement of regulations to insure the safety and health of the local population and ecology of the surrounding surface and underground source of potable water. In the U.S., almost all construction permits are preceded by preparation, review, and favorable analysis of the environmental impact that a new or renovated solid dosage form facility will have. Waste disposal is an integral component of the environmental impact study. The three classes of waste addressed are solid waste, sanitary waste, and process waste.

The U.S. GMPs state that, “Sewage, trash and other refuse in and from the building and...”
immediate premises shall be disposed of in a safe and sanitary manner," Sec. 211.50. In addition, “Trash and organic waste matter shall be held and disposed of in a timely and sanitary manner," Sec. 211.56(a). Sec. 211.48(b) indicates that, “Drains shall be of adequate size and, where connected directly to a sewer, shall be provided with an air break or other mechanical device to prevent backspihonage.”

■ The EU GMP primarily addresses drains. “Drains should be of adequate size, and have trapped gullies. Open channels should be avoided where possible, but if necessary, they should be shallow to facilitate cleaning and disinfection,” EU 3.11.

■ The Japanese GMP includes three statements with the added requirement to prevent contamination of the workroom. (1) “The area for manufacturing operations shall have facilities or equipment for the disposal of sewage and waste,” Ordinance No. 29, Art. 5, Par. 2, Item F. (2) “The area for manufacturing operations shall have facilities for the disposal of poisonous gases if generated in manufacturing any particular item,” Ordinance No. 29, Art. 5 Par. 2, Item H. (3) “The work room for weighing raw materials, formulating, filling or sealing drugs in the work area shall meet the following requirements: the sewage disposal facilities in the room shall be constructed so as to prevent contamination of the work room,” No. 29, Art. 5-2, Par 3, Item K.

Housekeeping/Cleaning and Maintenance of Manufacturing and Non-Manufacturing Areas

Tablets, and to a lesser degree, capsules often contain sucrose and other refined sugars. Refined sugars are used as sweeteners, fillers, and in tablet coatings. Pallets of sucrose and other sugars attract rodents and other vermin. These materials must be protected against infiltration by rodents and other insects. If they contain rodent droppings, and are used in the manufacture of solid dosage forms, the resulting products would be considered adulterated, and in violation of the FD&C Act. Recognizing the potential for non-compliance, the U.S., EU, and Japan have included regulations pertaining to the control of insects and rodents.

■ The U.S. GMPs state that, “Any building used in the manufacture, processing, packing, or holding of a drug product shall be free of infestation by rodents, birds, insects, and other vermin,” Sec. 211.56. “There shall be written procedures for using suitable rodenticides, insecticides, fungicides, fumigating agents, and cleaning and sanitizing agents in a manner that will prevent contamination,” Sec. 211.56(c).

■ The EU GMP states that, “Premises should be designed and equipped so as to afford maximum protection against the entry of insects or other animals,” EU-3.4.

■ The Japanese GMP addresses this issue as, “The area for manufacturing operations shall have facilities for the control of dust, insects, and rodents,” Ordinance No. 29, Article 5, Par. 2, Item D.

Building maintenance includes housekeeping, in addition to the physical cleanliness of ceilings, walls, and surfaces. Surfaces are further subdivided into product contact and non-product contact surfaces. Product contact surfaces include manufacturing, packaging, and testing (laboratory) equipment. Written procedures, usually in the form of Standard Operating Procedures (SOPs), are prepared and referenced for the various classes of equipment that require both cleaning and maintenance.

■ The U.S. GMPs state that, “Any building used in the manufacture, processing, packing or holding of a drug product shall be of suitable size, construction, and location to facilitate cleaning, maintenance, and proper operations,” Sec. 211.42(a). “Any building used in the manufacture, processing, packing or holding of a drug product shall be maintained in a good state of repair,” Sec. 211.58.

■ The EU GMP addresses this issue with the following statement: “Premises should be carefully maintained, ensuring that repair and maintenance operations do not present any hazard to the quality of products. They should be cleaned and, where appropriate, disinfected according to detailed written procedures,” EU-3.2. Further clarification is given. “Layout, design and operation must aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid contamination, cross contamination, and any adverse effect on the quality of the product,” Article 8, Par. 2.
■ The Japanese GMP addresses the issue too. “The area for manufacturing operations shall be adequately lighted, illuminated, ventilated and cleaned,” Ordinance No. 29, Art.5, Par.2, Item A.

Facility Utilities
A solid dosage form facility houses numerous pieces of automated, mechanical equipment used in the manufacture, filling, and packaging of drug products. As designed, these pieces of equipment require the support of utilities.

According to the ISPE Baseline Guide for Oral Solid Dosage form facilities, “utility systems that come into direct product contact should be designed, constructed and commissioned to provide material which meets a predetermined specification and prevents contamination. Utility systems which do not come into direct product contact should be designed and constructed in compliance with applicable codes and standards.” Each of the three GMP guides address utilities as set forth below.

Lighting
■ The U.S. GMPs state that, “Adequate lighting shall be provided in all areas,” Sec. 211.44.
■ The EU GMP addresses this with the following statement: “Production areas should be well lit, particularly where visual online controls are carried out,” EU-3.16.
■ The Japanese GMP states that, “The area for manufacturing operations shall be adequately lighted, illuminated, ventilated and cleaned,” Ordinance No. 29, Art.5, Par.2, Item A.

Water System
■ The U.S. GMPs state that, “Potable water shall be supplied under continuous positive pressure in a plumbing system free of defects that could contribute contamination to any drug product. Potable water shall meet the standards prescribed in the EPA’s Drinking Water regulations,” Sec. 211.48(a).
■ The EU GMP states that, “Distilled, Deionized and, where appropriate, other water pipes should be sanitized according to written procedures that detail the action limits for microbiological contamination and the measures to be taken,” EU-3.43.
■ The Japanese GMP states that, “The manufacturing facility shall have facilities for supply water of the quality or quantity needed to manufacture the drug (including cleaning water for facilities, equipment and containers),” Ordinance No. 29, Art. 5-2, Par. 5.

Though not specifically mentioned in the GMPs, in the U.S., compliance with NFPA, OSHA, NIOSH, or equivalent code is necessary to obtain a Certificate of Occupancy

Summary
Solid dosage form facilities are used for the manufacture of multiple, non-related products. The equipment is usually not dedicated to one product. Validated cleaning procedures containing documented cleaning methods by trained personnel is mandated by U.S. GMPs. Validated analytical test methods, documenting the lowest level of detection and lowest level of quantitation, are a necessary prerequisite to a sound cleaning validation plan. Physical separation of products to prevent mix-up is required by global GMPs. HVAC provides ventilation for personnel and must be designed to prevent cross-contamination between product through airborne transmission of particulates. Where fine particle dust is generated, specific precautions must be in place to avoid cross-contamination and facilitate cleaning.

For facilities where known cytotoxic drugs and radio pharmaceuticals are to be manufactured, the manufacturing areas and their air handling (HVAC) systems need to be separated from those used for other drugs. Exhaust ducts on facility roofs must be checked to insure that the exhaust from one system does not feed the intake duct of another system. Though not specifically mentioned in the GMPs, in the U.S., compliance with NFPA, OSHA, NIOSH, or equivalent code is necessary to obtain a Certificate of Occupancy.
of Occupancy. In-process material, finished products, and packaging materials must be protected against infiltration by rodents and other insects. A documented housekeeping, cleaning, and maintenance plan are necessary for regulatory compliance. Written procedures in the form of SOPs are necessary for reference to cleaning and maintenance procedures for equipment and the facility.

The overall conclusion that can be drawn from this paper is that reliance on the GMP regulations of a single governing body is not sufficient to assure adherence to all global requirements. It is recognized that, for the most part, the global regulations do closely match but there are enough differences that all of the regulations should be given due consideration when designing and constructing a facility to meet global cGMPs. Failure to do so could potentially result in a facility that is not compliant with one or more of the global regulations. The financial implications of non-compliance can be significant.

The pharmaceutical industry can truly be considered a global rather than a regional industry. Very few of the major pharmaceutical companies have all of their facilities within a single geographic location such as the U.S., Europe, or the Pacific Rim. Rather, Industry, in general, has facilities located throughout the world. As a result, it is a necessity that Industry be cognizant of the appropriate regulations not only where they are headquartered but also where they have facilities located worldwide. This should provide the pharmaceutical companies with the advantage of having a basis of regulatory knowledge that is global in its scope. This in turn should enable these firms to minimize the risk of any facility they construct anywhere in the world.

Because the pharmaceutical industry is a global industry, logic would dictate that uniform regulations apply. The need for uniformity in regulatory requirements has been recognized by the worldwide regulatory bodies, as well as Industry. It can be assumed that uniformity is not far-off based on such advances as the ICH, ISO, the MRA, etc. However each nation, or group of nations, still have their own idiosyncrasies that must be overcome before true uniformity can be achieved. Until this point is reached, it is important to acknowledge that there are different regulatory bodies throughout the world that must be satisfied in order for global compliance to be realized.

The authors would like to acknowledge the contributions of Alicia Sardar and Carl Sullivan in the preparation of this paper.

Suggested Reading