PDHonline Course K119 (5 PDH)

Packaging Line Engineering and Operations for the Pharmaceutical and Similar Industries

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2020

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2006

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Course Content

Introduction

Production that is automated is essential in today's environment, with packaging lines being a prime example of this technology. Do packaging operations fascinate you but seem to be too far removed from your experience to be understandable? Would you like to know more about the fundamentals of packaging engineering operations? Or are you already familiar, but would like to understand its application to the Pharma industry? This course will cover the fundamentals of this subject (yet comprehensive), focusing on the Pharma but relevant to similar industries. Although not intended to be a highly technical course on machine design and sophisticated controls, we will explore the essential elements of understanding integrated packaging line engineering and operations necessary for the engineer involved in the industry. The perspective of the course is from the specifier's point of view primarily, and not the machine designer.

Equipment Justification

Like any project, the Owner has a need or a series of needs to be met when embarking on a packaging equipment project. There are several drivers that are relevant as well as key considerations for the project.

Cost of goods

The cost of goods sold is defined as the total cost required to produce a product unit for the market place. The lifecycle costs of the equipment will be a component of the cost of goods. The first cost of capital (via financing or meeting a hurdle rate), depreciation, property tax, and maintenance are all costs that will impact the bottom line and will eventually be passed to the

consumer. However, market forces will limit the cost of goods if one is to be competitive. Therefore, the cost of the equipment (in addition to other costs) must not price the product out of the market.

Meet volume

The equipment must meet the demand established by the market and operational efficiencies. To begin, the Packaging Engineer must understand the acceptable product per shift required. Then, he or she must apply efficiencies to determine total line speed and individual machine center line speeds. Unfortunately, mistakes are often made at this fundamental step, and there is considerable disappointment and financial implications when the installed line doesn't deliver. This topic is covered more extensively later in the course.

Reduce labor/payback

A primary driver for updating a new line as well as a key consideration for a new line is reduced labor. The cost of labor is a major component of the cost of goods – putting it simply, people are expensive. Companies will have differing payback periods, often determined by return on capital considerations, or expected longevity of the product, or life of a technology. If automation and machine centers have the potential of reducing labor, they should be considered. The following is an example of a cost/payback analysis, although simplified for demonstration purposes.

Example:

Consider Machine Center A that costs $100,000 and requires 3 people to operate. Assume the cost per person is $40,000 per year. Machine Center B costs $260,000, but only requires 1 person to operate. Assume for simplicity that all other lifecycle costs remain the same. Which Machine Center should you choose if the company requires a 3-year payback on equipment?

First, what is the difference in first cost of the two options? $260,000 - $100,000 = $160,000. Next, calculate the cost savings per year = (3 people – 1 person) * $40,000 = $80,000. Then calculate the number of years to payback = $160,000/$80,000 = 2 years which is less than the 3 year target. Therefore, choose Machine Center B.

While the decisions as to which option to choose are often more complex, this is the general approach used to make a business decision whether to modernize a packaging line.

Safety or Regulatory need

Another key driver for designing, selecting, or improving existing equipment results from a Safety or Regulatory need. Perhaps a machine center is determined not to operate safely – this could be from ergonomic concerns, machine safeguarding, or emissions. Also, there could be an FDA regulatory requirement. Perhaps it is determined there is a quality element lacking, or regulations are increased, or product is to be sold in another country with stricter requirements. All these can cause a packaging line project.

Utilization

Usually, with higher output rates there come higher equipment costs. Therefore, equipment must be selected to meet the actual as well as projected demand but not be conservatively overstated. Also, equipment costs are more quickly absorbed and affect the bottom line better when the equipment has a high usage rate. For example, unless there is a redundancy requirement, it is better to have one line fully utilized than two 50% utilized.

Flexibility

When specifying equipment, it is necessary to understand the flexibility required for the line. Often, lines are dedicated to a single product or product line due to technological limitations or regulatory demands. However, others (especially for consumer health products) must function for a variety of products and container sizes. This must be included in the scope/spec (URS or User Requirement Specification and FRS or Functional Requirement Specification)[1] provided to the equipment manufacturer. However, be careful not to specify unnecessary versatility. Usually, with more versatility comes higher cost, complexity, less efficiency, and lower line speed. Other considerations are important for multi-use lines, such as line clearance (capability of being able to remove any remaining product or packaging

[1] URS is a document that explains more of the "what" the equipment is to do and fundamental deliverables, and the FRS builds on the URS, adding detail to further address the "how." The URS is a high level/low detail document. Sometimes, URS and FRS are combined. This will be discussed in more detail later in the course.

components from the equipment), cleaning, and identification equipment/vision systems. When calculating line speed, include change time.

Ways to meet the need

Once a need is established, there are four primary ways to meet the need. The first is to outsource the need, a common approach today. This involves finding a contract packager. Often, this option is chosen when a third party is more cost effective, capital or facilities aren't available, or the success of the product launch is uncertain (i.e. the introduction to the market is a trial launch.) The second is to modify the existing equipment. This option may be chosen when the line generally meets requirements but needs improvements or changeover for another product. Another option is to do an equipment rebuild, which will restore or exceed original performance and facilitate integration of modern technologies. However, inventory builds are necessary to avoid missing product demand. The third option is to purchase new equipment, which is the primary focus of this course. And the fourth is to purchase refurbished equipment.

So we have reviewed key drivers and considerations needed for a packaging line project. Before we expand our study further, let's next review the types of packaging components typically utilized on a Packaging Line.

Packaging components

Packaging Components are items associated with packaging the product, but not the product itself. The following are typicals:

Primary

The first type of component is described as "Primary." These are the components that primarily enclose or encapsulate the product, often touch the product, and provide necessary initial closure. These are typically as follows:

- **Bottles/caps**

Bottles are the most common items we think of when it comes to primary components. Bottles are typically (and more commonly today) plastic although some remain glass, and can be used to store a variety of materials including liquids and tablets or capsules. Bottles are closed with a cap, either pressed or screwed on. Often, there is a tamper evident seal placed – an

induction sealer may be used to attach a metallic cover over the bottle opening prior to the cap, accomplished via a resistive current that effectively melts the top of the bottle, adhering it to the seal.

- **Tubes**

Tubes are used to encapsulate ointments and creams. These often come in preprinted tubular shapes handled on equipment that is capable of crimping one end providing the necessary assembly for end caps. Some product requires a hard shape, such as lip protectant, into which molten product is filled.

- **Thermoform**

Themoform equipment enables the container to be formed by the machine by distorting film under pressure and heat, inserting the product (often capsules or tablets), and adhering a backer to fully enclose the product.

- **Pouch**

Pouches are used to enclose dry product typically, and are often used for small volumes. You see these at the convenience store when needing a couple of over the counter painkillers, for example.

- **Form-Fill-Seal (FFS)**

This technology involves forming a package on the same machine that fills the product. This is a typical application for flexible packaging. The product takes the form of the formed package. This is commonly used for suppositories, for example.

- **Other**

There are as many varieties of primary components as there are ideas for product forms. There are mechanical devices, tubes, and other creative and cost effective means of protecting the product primarily.

- **Sterile**

The most common sterile primary packaging components are glass vials, made of type I glass for SVP's (Small Volume Parenterals). You are probably familiar with these, which are commonly used when receiving a vaccination (inserting a syringe needle in the top stopper, extracting the product.) Other forms include pre-filled syringes, ampoules (a sealed glass container with a long neck that must be broken off), and LVP's (Large Volume Parenterals, typically holding 100 ml or more) in bags or bottles (type II glass). The following are

illustrations of typical SVP containers:

Labels

Depending on the individual company, labels might be considered primary or secondary components. Whatever the designation, they remain essential in identifying the product as well as presenting drug facts per FDA requirements. Labels can be directly printed on the package (not common), or be applied from preprinted material. Preprinted materials can be directly applied or require equipment to apply adhesive.

Secondary

Secondary Packaging includes boxes to enclose the primary container. This is necessary for ease of shipping, to protect the primary enclosures, and for product identification. Especially for OTC (Over the Counter) type products, this is the packaging element which the customer first sees.

Tertiary Packaging Components

Typically, additional enclosures are necessary to further protect the product and enable shipping. These are usually boxes or wrappings, also called "shippers." Labels and barcodes are applied to enable further identification and to facilitate shipping and tracking. RFID (Radio Frequency Identification) is becoming more familiar and a required technology by some wholesalers, and are applied similar to a label.

So far in this course we have reviewed primary drivers, considerations, and packaging

forms typically used. Next, let's look at typical machine centers utilized in an integrated line.

Typical Machine Centers

Rarely are packaging lines made up of a single machine center. Rather, packaging lines for most products are made up of discrete equipment integrated to perform the complete or partial packaging operation. In this section, we will review the machine center primary categories that make up a complete line. Often, multiple vendors provide individual machine centers, but a single vendor or integrator might provide line assembly and integration if an Owner's internal resources aren't available.

Primary packaging components and product introduction

The goal of this category is to provide Primary Components and Product to the packaging line. There are multiple functions required for this machine center, which may comprise of multiple subcenters.

First, there is a sorting requirement, or Primary Component Supply. The Primary components must be received by the center, properly fed and aligned. This requires sorting capability to properly align. There needs to be means to reject improperly aligned or misplaced components, often accomplished by mechanical methods and vision systems.

Next is the Product Supply, where product is supplied from Product or Solution Prep equipment or operations. Often, product is provided to Product Fill in its finished form, or it will need to be prepared for fill. Of critical importance is sterile product, which must either be maintained in or changed to a sterile state prior to fill (with the exception of products that receive terminal sterilization.) Typical sterilization techniques of the product prior to fill include heat, irradiation, and most commonly filtration through a 0.22-micron filter which is sufficient to remove most bacteria and molds (but may let viruses and mycoplasmas through). Such filters should be validated that they repeatedly remove viable microorganisms from the sterilized process stream. Filters should be pre/post-bubble tested to confirm integrity. Once the product is sterilized, it is protected in a sterile state and packaged. Tanks holding or processing sterile products should be maintained in a pressurized state or otherwise sealed to prevent contamination from microbes; valves should be steam sterilizable in some applications. However, some products cannot be sterilized prior to filling, and certain process steps must be

undertaken in closed or class 100 clean room environments (this means there are no more than 100 particles 0.5 micron and larger in a cubic foot of air), also called "Critical Areas."

Product fill

Next we need to fill the product into primary components and enclose. There are several types of product that we might need to fill. The first is solid dose, which can include a variety of solid dose forms such as tablets (often mistakenly referred to as "pills"), capsules, gel caps, etc. In this method, the solid form is introduced into the containers at a fixed quantity per container or weighed. Liquid product is also common, where product is introduced into containers. Also common are ointments and creams, usually filled hot to minimize viscosity and facilitate flow fill. Cooling capability is also needed. Another but less common form for pharmaceuticals (common for foods) is extrusion. Most complex are Sterile/Aseptic products. While most products are not required to be sterile, some applications require a more rigorous process to ensure sterility (it depends on the product and its applications).

What do we mean by Aseptic? Aseptic simply means there are no microorganisms that can cause infection in the patient. Unlike products that are terminally sterilized (the preferred method by major regulatory agencies), an Aseptic operation maintains acceptable sterility at critical steps of the manufacturing process (when sterile filtration or other means are not possible) and filling operations (when terminal sterilization is not an option). When the product can be terminally sterilized (autoclaving the most common method), Aseptic processing is not necessary. Aseptic processing is common for parenterals (injectible drugs.)

Whether produced in an Aseptic manner or terminally sterilized, parenterals must be sterile in their final form to avoid problems for the patient. Products that are not sterile may contain pyrogens ("an agent capable of inducing an increase in body temperature; usually refers to fever caused by bacterial endotoxins.")[i] An Endotoxin is "cell wall debris" from bacteria." [ii] These may include bacteria such as E. coli, Salmanella, and a host of other ugly bugs and pathogens. Whereas drugs such as OSD's (Oral Solid Dosage) typically do not require sterility since the body's natural defense mechanisms engage after ingestion, parenterals are injected intramuscularly (I.M.) or intravenously (I.V.) and bypass the defense mechanisms and are therefore more critical.

Other forms of products that require special care are Hazardous/Potent compounds,

which may require glove boxes and other means of worker protection.

Product Enclosure

The next machine center (often combined with the previous) is Product Enclosure. Here, caps are applied to bottles, backers to thermoformed packages, stoppers applied to vials, and other methods are used to seal the product. Proper torques on caps and other means to ensure avoidance of leakage are essential. Tamper proof means are also applied routinely to minimize the risk of secondary (and sometimes intentional) contamination. (See previous discussion on induction sealers, for example.)

Product Labeling

Often the product is labeled by a separate machine center. This can be performed by apply labels, often with adhesive, or a shrink-wrap label.

Date and lot coding

Equipment is needed to identify the lot that is contained in the package, as well as the date of package. This is a regulatory requirement, and is practically needed to trace product back to batch records. This is especially useful when tracking a complaint, performing a recall, or a general product investigation.

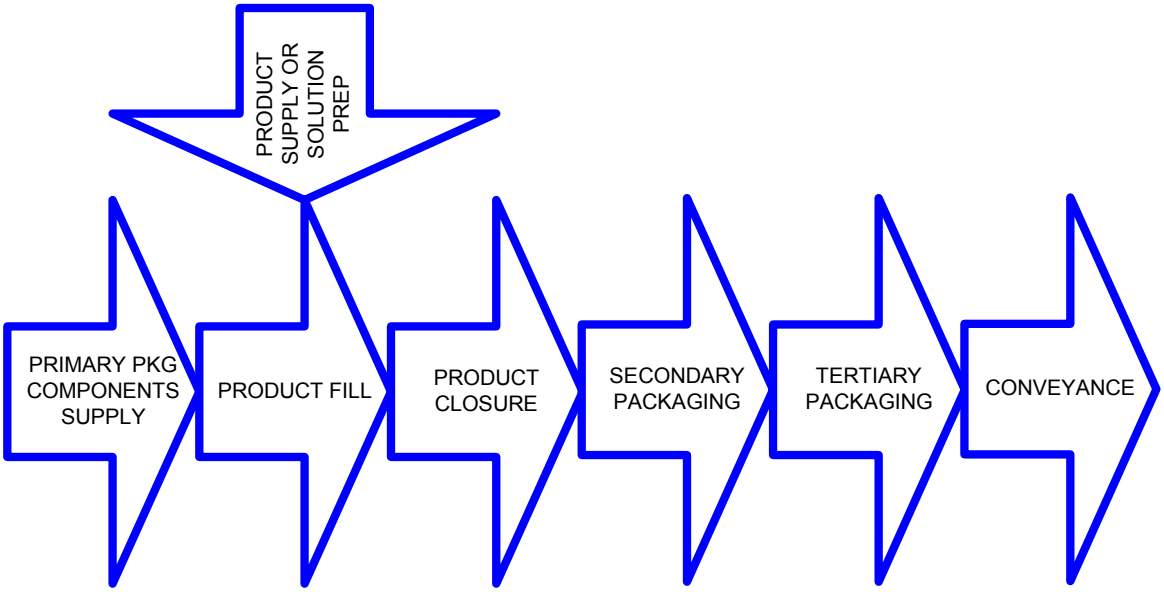
Secondary packaging (Cartons, etc.)

Where secondary packaging is required, specialized equipment is needed to assemble the carton, insert the product contained in the Primary package, seal, and organize for shipping or tertiary packaging. Then, the product proceeds to Tertiary Machine Centers if required, where the cartons are placed in boxes or other containers, or are simply wrapped. Other specialized equipment may include bundlers, box tapers, and box labelers. Once the product is ready to be shipped, it is generally placed on a pallet – either manually or automated (sometimes with robotics.)

Conveyance

After the product is palletized (or prior if palletizers are remote from the Line), product is

transferred to intermediate storage or the truck. In the Pharmaceutical industry it is common to "quarantine" product until it is released for sale by Quality Assurance (QA). Conveyance means can include manual fork trucks, conveyors, or AGV's (Automatic Guided Vehicles).



BLOCK DIAGRAM OF TYPICAL PACKAGING LINE

Other

There are many other machine center categories, a few of which are mentioned in the following. It is important for the Packaging Engineer to fully understand the product being packaged and identify specific applications needed.

- **Autoclave** – Used to sterilize product contact items, and has been defined as follows[iii]: "An apparatus into which moist heat (steam) under pressure is introduced to sterilize or decontaminate materials placed within (e.g. filter assemblies, glassware, etc.). Steam pressure is maintained for pre-specified times and then allowed to exhaust. There are two types of autoclaves:
    1. Gravity displacement autoclave: This type of autoclave operates at 121ºC. Steam enters at the top of the loaded inner chamber, displacing the air below

through a discharge outlet.

2. Vacuum autoclave: This type of autoclave can operate with a reduced sterilization cycle time. The air is pumped out of the loaded chamber before it is filled with steam"

- **Lyophilizers** - Used to freeze-dry product. This is to add additional stability to products when required, which involves freeze-drying liquid after being placed in vials but prior to complete stoppering. Often, biological materials require freeze-drying for better stabilization. Certain products, such as proteins, don't react well to heat, eliminating the application of terminal sterilization. Freeze drying is often used for vaccines, pharmaceuticals, and blood products. A medical provider will reconstitute the product with a suitable solvent (usually WFI or Water for Injection) prior to use. Here is how Lyophilization occurs. During the fill process, the vial is partially closed. Therefore, it must be maintained in an Aseptic Class 100 environment until lyophilized and finally sealed. This can present a challenge that must be thought through when designing a sterile packaging operation. Lyophilization consists of three distinct processes – freezing, sublimation, and desorption. Sublimation involves vaporizing a solid and condensing it without its having passed through a liquid state. Desorption involves "the release of adsorbed molecules, particles, or cells into the surrounding medium."[iv]
- **Blow/Fill/Seal**: Another technology available for sterile applications is BFS (Blow/Fill/Seal). This involves forming a parison (a tubular form) from a plastic polymer resin, inflating it, filling it, and sealing it in a single operation. However, at the present this method cannot accommodate Lyophilization.
- **Sterilizers**: Equipment used to sterilize product, including terminal sterilization (after primary packaging).
- **Vision systems**: Automated vision systems can be used to reject product, and to record lot and date codes, as well as facilitate automation.
- **Printers**: Printers can be used to imprint important information such as lot and date codes on primary components at a high speed.
- **Accumulation**: Often, an individual machine center will jam or need to run intermittently. This can result in other machine centers cycling on/off. To avoid this, accumulation means are often provided to allow the accumulation at a specific step. Accumulators (or buffers) are

also useful at increasing line efficiency, although excessive buffering may be an indication of poorly designed machine centers. Finally, accumulators are also placed after equipment that must run continuously and cannot be shut down. In the food industry, an oven is an example of equipment that can't be shut down.

- **Reject**: Often is necessary to reject product for a variety of reasons at different machine centers. This can be because of poor or missing labeling, improper orientation, improper fill volumes, detected metals, or other on-line problem identifiers. Rejection is accomplished by mechanically or pneumatically actuating the product off the line into a reject bin.
- **Glove box/Isolators**: Barrier Isolators are a good application (in some cases) in lieu of open Class 100 areas (in the case of Aseptics) or where there are hazardous compounds. Barrier Isolators totally contain the product in a protective state consistent with Class 100 requirements. Not only must the product be protected, but also the worker when there are hazards of cancer, mutation, or developmental/reproductive problems resulting from product exposure or general sensitive to API's (Active Pharmaceutical Ingredients). Barrier isolators (Level II) are especially helpful in this application, and avoid the use of pressurized suits. Barrier isolators also can simplify/minimize the requirement for clean rooms, which avoids first-cost as well as the complexity and expense of operating and working in more restrictive clean room environments. Background environment requirements are relaxed in this case. In addition, Barrier Isolators can address an OSHA preference to rely less on PPE (Personal Protective Equipment). However, there are many challenges with this technology, both to initially design and install, as well as on-going operations. Some of the challenges that you need to consider when designing and developing operational requirements for Barrier Isolators are as follows:

    1. Issues associated with transfer methods
    2. Leak integrity design and testing
    3. Maintain Aseptic (Class 100) environment
    4. Cleaning and sterilizing (Hydrogen Peroxide Vapor or Chlorine gas are common methods, but the workers must be protected.)
    5. Run speeds are often lower in Barrier Isolators, such as 100 vials/minute or lower.
    6. How to handle potent products while simultaneously protecting the

product

7. High first-costs
8. Ergonomic problems/access
9. Difficulty of maintenance access

Another method of having better control in the Aseptic environment is to provide a Restricted Access Barrier System (RABS). This simply separates the operator from the Aseptic environment to minimize the risk of introducing operator contamination. However, this is not a self-contained barrier isolation system, and Aseptic conditions must be maintained by other means.

- **Inserts**: There can be a variety of non-product items that requires insertion with primary or secondary components, such as cotton, dosing cups, etc. Inserts also include written product data and dosing instructions.
- **Coupons**: To address marketing initiatives, coupons are often inserted with Secondary packaging components.
- **Check weighers**: At some point on the line, there must be means of verifying fill volumes, either by level detection and commonly by weight.
- **Metal detectors**: These are installed to ensure metal hasn't found its way in the product.
- **Robotics**: Where typical machine design applications will not suffice and where complex motions are required, robotics may be necessary. Robots are also useful when high placement accuracy is required, or in dangerous environments. When specifying robots, include axis of movement considerations and type/extent of rectilinear motion required. Robots typically consist of a main frame, along with a mast and hand, all controlled by a motor. However, more traditional packaging methods often are more cost effective, require less maintenance, and offer faster run rates.

Equipment Cleaning

The Packaging Engineer must be aware of the cleaning requirements for the equipment, as well as the method. Are methods manual, automated, or mixed? Is the product sterile or nonsterile?

Nonsterile

Just because a packaging operation does not require the end product to be sterile we are not released from needing clean conditions. The Line should not cause any foreign matter to enter the product from its operation. In addition, the Line should be designed in such a manner that it is easily cleanable, and Line Clearance is capable of being maintained. (Line Clearance is verification that another product and components are cleared from the Line prior to using it to package another product or size.) The fabrication materials of the line are important as well, and should not result in flaking of paint, friable degradation, or contain other materials that are reactive or absorptive. Corrosion should also be inhibited, thus the widespread use of stainless steel in Pharmaceutical applications.

Decisions also must be made regarding extent of manual versus automatic cleaning. Clean-in-place (CIP) is sometimes used to automatically clean vessels and pipes. Steam-in-place is also used in Sterile applications, discussed as follows.

Sterile/Aseptic

Careful consideration must be given to all Aseptic equipment. Filling equipment must be designed to be cleanable. CIP/SIP is sometimes used (Clean in place/Sterilize in place). Moist heat is common for sterilization. (Note: Sterilize is different from Sanitize. Sterilize means to destroy viable organisms and spores, whereas Sanitize reduces viable organisms to an acceptable level.) CIP can be problematic in the Aseptic area, so proceed with caution. Endotoxins on equipment surfaces can be inactivated by heat, and removed by cleaning procedures; however, autoclaving is preferred for product contact parts. The key to controlling bioburden is to adequately clean, dry, and store equipment. Therefore, it is essential that the design of such equipment facilitate this by being easy to be assembled/disassembled, cleaned, and sanitized/sterilized.

Safety

Safety is obviously a key element to incorporate in the design of a Packaging Line. Safety can be considered to extend to two areas. The first is safety for the operating employees. Safety is expensive – there are medical costs, lost time, down time, and potential lawsuits. Secondly, the Line must package safe products, or not add any deleterious elements to the product that will detrimentally affect the consumer. “Do no harm” is the mantra. Product

liability lawsuits have virtually crippled many companies, and continue to add considerable cost to our products and medical costs in general. Obviously, safety in both areas is essential, not only because of the cost but it is the right thing to do. The following are a few safety aspects related to employee safety:

- **Machine guarding, pinch points**: OSHA has considerable requirements for machine guarding. In addition to physical guarding, this includes automatic shut-offs when machine guards are opened. The equipment must not present a hazard of pinch or "pull-in" when guarded. The following are the major hazards from machinery:
    - Nip points: This occurs when two moving parts come together that can pull in fingers, hair, or clothing
    - Shear points: This is where shearing or cutting actions occur
    - Pinch: This is where body parts could become pinched or crushed.
    - Electrical hazard: Shocking could result
    - Heat, cold, or other energy releases

  The following are a few specific considerations for Machine Guarding:
    - Design equipment to avoid the necessity of reach in to "clear" equipment
    - Incorporate proper Lockout/Tagout practices
    - Be sure to guard parts of the machine that move, including flywheels, pulleys, belts, couplings, chains, cranks, and gears
    - Design equipment to prevent the operator's body or clothing from coming in contact with hazardous moving parts
    - Design equipment to ensure no objects can fall into moving parts
    - Design for safe lubrication without moving safeguards if possible (as a side note, specify appropriate lubes and oils that do not present a hazard to the product)
    - The following are the typical types of guards:
        - Interlocked Guard
        - Adjustable Guard
        - Self-Adjusting Guard
- **Safety-conscious controls**: When designing controls, think how operating them can minimize a safety risk. For example, consider designing Two-Hand Controls, which

necessitates constant and concurrent pressure to activate the equipment

- **Ergonomics**: This extends to safe physical work practices. The equipment must be accessed and controlled with minimal effort, avoid excessive reaches and manual lifts, and generally cause no harm to the operator. Lift assists for rolls, hoists, etc. should be considered where heavy loads are to be manipulated.
- **Dust explosions**: When handling organic powders, dust can explode under certain conditions. Ingredients should be evaluated in the laboratory to determine the extent, if any, that an explosion could occur and its severity. Means must be taken to mitigate if present. Nitrogen blanketing is common, but this can present other safety concerns if not properly engineered.
- **Flammables:** Similar to Dust explosions, if the product is a liquid and contains flammables, it must be evaluated to determine if it has a flashpoint such that it needs to be handled as a flammable liquid. If flammable, electrical classifications change, as well as the building classification in which it resides. Classified electrical components and barriers for control circuits may be required.
- **Potent compounds:** This addresses impact to workers chemically or biologically. The product may not be suitable for uncontrolled exposure. Even apparently mild active ingredients may present an exposure problem when concentrated or when exposure extends over time. See previous section regarding glove box operations.
- **PPE:** Personal Protective Equipment (PPE) may be required. This can include ear, eye, respiratory, and skin protection. However, as much as possible, the need for PPE should be "engineered out" of the system. Remember to include noise limits in your URS/FRS; however, sometimes it may be cost or practically prohibitive to reduce sound below a certain level. Also remember hand protection, a common source of injury from packaging operations (cut resistant gloves are recommended when use box cutter knives, for example.)

But as mentioned above, consideration for product protection for the end consumer must also be included. The following are some key considerations for protecting the product:

- **From the environment:** At a minimum, product must be protected from absorbing excessive particulates or bioburden if it is absorptive or sensitive to such at the time of

exposure during fill operations. The closer to sterile the product must be, the more stringent the engineering. For nonsterile, practices include fill suites with properly filtered HVAC supply air, or microenvironments (pressurized and filtered containment around open product areas), or dust covers for less sensitive products. You must understand the sensitivity of your product before specifying the appropriate containment. (Sterile is covered elsewhere herein and in a separate course.)

- **From people:** People are the primary source of contamination typically in Pharmaceutical environments. We continually slough off skin particles, plus expel through our breath. Therefore, it is important to work with product development to understand the extent to which gowning is required. The closer to sterile, the more stringent the requirements. The more garb, the simpler the equipment must be to operate (have you ever tried to activate controls through layers of gloves and gowning?)
- **Aseptic/sterile:** As noted previously, aseptic simply means there are no microorganisms that can cause infection in the patient. Therefore, the equipment should not introduce contaminates, but maintain a sterile condition as well. This is adequately covered elsewhere herein and in the course, "The Fundamentals of Aseptic Pharmaceutical Engineering."
- **Line clearance:** This topic has been covered elsewhere in this course. However, this is often overlooked or not adequately covered in the specifying and designing of packaging equipment. Design the equipment where product or components cannot easily "hide," and where such is easily visible when performing a line clearance walk down. Design the equipment and the integrated line such that LOTO (Lock-out/Tag-out) is easy and can be safely performed, and machine guards can be opened if needed to visually confirm proper line clearance.

Technologies

The packaging engineer must be familiar with technologies on the market today. Except for machine manufacturers, the packaging engineer will usually act more as an integrator than a detailed designer. However, the effective packaging engineer will have a firm grasp of engineering fundamentals of machine design and state-of-the-art technologies. Expertise is required to understand, specify, and troubleshoot packaging lines. Remaining current with technologies available requires attending trade/vendor shows, networking, professional

organization activities, and continuous learning. The following are some quick thoughts regarding technologies.

- **Controls: PLC's/SCADA:** Microprocessor controls offer virtually infinite possibilities for monitoring and controlling variables on equipment, such as settings, throughput, weights, speeds, etc. Programmable Logic Controllers are dominant in packaging line control. These are robust and flexible, as well as relatively easy to maintain. Often, individual machine centers contain their own PLC's and interface with an integrated line panel. SCADA (Supervisory Control and Data Acquisition) is also an approach to create effective user interface, remote control, tracking, trending of line efficiencies, and recipe commands. Understanding ladder logic is essential. Sensors and devices must be accessible for maintenance and calibrations. More detail of control technologies is beyond the scope of this course.
- **Robotics:** As mentioned previously, robotics may be required where complex motions are required, but should be considered at lower speed sections of the line. For example, palletization using robots is often an effective solution.
- **Typical machine design considerations**:

One of the fascinating aspects of Packaging machinery engineering are the creative methods of solving problems using a complex array of movement from gears, cams, belts, conveyors, actuators, etc. The technology covers the spectrum of machine design. As noted before, machine design is beyond the scope of this course, but the individual performing the design must be well versed in all aspects of electro-mechanical engineering as well as be familiar with latest technologies.

Machine motions are caused, timed, and controlled by many means. Movement is caused by mechanical actuation, including cams, chains, levers, gears, and push rods. These movements can also be caused by electrical means (such as timers, micro-switches, relays, etc.) As well, hydraulic or pneumatic means are available, the latter being more common in the Pharmaceutical industry (particularly near product) to avoid contact with fluids.

Again, most packaging engineers (except for equipment manufacturers) will spend less time designing machinery and more selecting/integrating. The following are a few key considerations when selecting machinery:

- Equipment should operate with a minimum of vibration, noise, and problems

  - Flow of components and product should be smooth and with minimum directional change
  - Equipment must be accessible for maintenance and line clearance
  - Ensure proper machine guarding
  - Ensure materials of construction are not absorptive, reactive, or friable to the product
  - Rotary mechanical motions are preferred over reciprocal where possible
  - Heavy drive trains should be located low on the equipment with easy maintenance access.
  - Ensure safe lubricants
  - Avoid machine components over product that could permit lubricants or debris to fall
- **Rotary versus Straight Line:** Fillers, cappers, and labelers can be designed in rotary or straight-line configurations. Rotary motions are very common and provide continuous motion for such operations, whereas straight line operations index/stop a container in a station to perform a function. Generally, rotary machines operate at higher speeds that do inline, intermittent machines. Rotary equipment involves removing a component from a straight conveyor with a starwheel, passing through a turret, and then returning it to a straight conveyor for the next operation.
- **Custom Machinery:** As much as possible, use off-the-shelf or minimally customized equipment. But occasionally none exists on the market. This can also occur for integrating elements between machine centers.
- **Filler Technology:** Often, the filler represents the critical machine center. Filler equipment must be chosen based on performance requirements, and especially the type of product being filled. Fill accuracy requirements often involve statistics. Remember to include your fill accuracy/limits/ranges in the URS/FRS. The following are typical categories for filler types:
  - Discrete Items: This includes tablets, capsules, and other "dry" items. Often, such items are counted by the filler before closure. Other means of confirming fill quantity are by volume and mass.
  - Free Flowing Powders: This includes powders or granules that are free flowing, and form a relatively flat cone when dumped on a flat surface. Simple free fall gravity feeders work well for this. Methods of confirming fill quantity can be similar to the previous.

- Wet Product: This can include product that is liquid at room temperature, or products that are filled heated but partially or wholly solidify at room temperature. A wide variety of technologies are available based on the product and viscosity. These include metering, vacuum fillers, gravity fillers, piston fillers, etc.
- Auger fillers: These are for products that are not free flowing.

- **Specification Checklist:** The following is a checklist of typical design considerations required for a machine center, which should be included in the URS/FRS as well as RFQ's (these represent typical considerations and your applications may differ):
  - Basic Performance Requirements
    - Theoretical Speed (CPM or Units per Minute)
    - Maximum Reject Rate over a shift
    - Operating Efficiency (machine center, over a shift)
    - Required tolerances (fill volumes, etc.)
    - Packaging specifications (cap torque, etc.)
  - Include information on product and components
    - Component specifications
    - Product listing and volumes of fill required
  - Overload and Run-out: Overload is protection necessary to prevent equipment damage due to jamming. Run-out addresses proper machine responses when components or product aren't available.
  - Cleaning Requirements
  - Safeties and emergency stops, and machine guarding
  - Inspection and Rejection Requirements/Technologies
  - Functional Operations and Requirement – define as much as possible the functionality aspects of the equipment. Be certain to answer, "What functions are required of the equipment?"
  - Computer/Control System Integration and Requirements, as well as human interface/screen shots (if available)
  - Integration with other equipment or transfers
  - Changeover requirements, if any
  - Materials of Fabrication

- Maintenance Considerations
- Spare Parts
- Machine access and undercarriage clearance
- Safety/Ergonomic Requirements
- Utility requirements
- List any standard specifications or preferred components
- Documentation Required
- Shipping/Delivery
- Any installation assistance needed
- Factory representative startup and assistance
- Commissioning, Qualification, and other checkout required
- Standards (OSHA, Electrical codes, etc.)
- Training
- Warrantee requirements (remember to include parts and labor. One year is typical.)
- Include any service or PM agreement requirements
- Responsibilities for utilities. (Note: A common way to delineate responsibilities is to provide utilities to a chase, and require the vendor to connect from the chase to the equipment.)
- Responsibilities for component and product prep or supply (Note: It is often a practice to delineate the scope such that product is brought to a connection on the machine center by others, but component supply aspects may be included in the vendor's scope.)
- Quotation procedures

Utility Support

- **Utility Matrix**: It is important to identify early the utilities required for the entire line. A simple table or spreadsheet is useful for this. Each required utility should be identified per machine center. Include the quantity and units required. For example, indicate the SCFM of compressed air. For electrical, indicate the breaker size and FLA (Full Load Amps), and include the diversity for proper service sizing. Often, vendors and integrators will grossly

overstate the electrical demand, not factoring in diversity, which results in oversized feeders and overstated HVAC heat loads. (Diversity factors reflect actual running loads, and are not the summation of breaker amps.)

Packaging Line Utility Matrix

Equipment Description	Electrical				Compressed Air		Other	Other	Notes:
	Phase	Voltage	Breaker Amps	FLA	SCFM	PSI			
TOTALS									

Total Line Diversity

Utility	Factor	Total load with Diversity
Electrical		
Compressed Air		
Other		
Other		

- **Electricity:** Specify the voltage and amps required for the equipment. Consider the available current. For example, don't specify 3-phase if it isn't available in the facility (rarely a case in most facilities.) Avoid individual transformers on machine centers as much as possible which results in inefficiency and heat load to the space. Also, watch out for foreign frequencies (hz) and voltages, which may require special transformers when it arrives on site, and may be more complex to maintain and acquire parts.
- **Compressed Air:** Compressed Air is often viewed as an "easy" and virtually "free" commodity. However, CA is very expensive to produce – it is compressed, dehumidified, and filtered. While it is useful for pneumatics and actuation, using CA for panel cooling and blow-offs is inefficient – consider other technologies. If you aren't specific with this, vendors may take the "easy" route and provide excessive pneumatics. Remember to include any environmental requirements for CA if it can come in contact with open product. Most companies have some limitations on hydrocarbon limits, viable and nonviable particulate, and moisture content. Also ensure there is available working pressure for the design.
- **Other gasses (ex. Filtered Nitrogen)**: Include other gases, such as nitrogen, etc. and include life safety issues.
- **Hot/cold water:** Water is occasionally needed for cleaning and heating/cooling.
- **Clean steam:** Clean Steam is required for Steam-in-place (SIP). This is produced in separately from house steam. Clean Steam is also sometimes used for HVAC humidification.
- **Purified Water or Water for Injection (WFI):** This must be produced and distributed such that microbial growth is prevented. This often includes circulating above 70^{o}C.

Determining Line Capacity

Let's slow down for a moment and consider the topic of determining line capacity in more detail. As noted previously, this is a fundamental step which if incorrectly applied can result in the project not delivering the product volume needed. To begin, the Packaging Engineer must understand the required output of the entire line or "Throughput." Some have made the mistake of stopping here, and specifying each machine center to meet marketing demand alone. However, one must consider many other factors before specifying individual machine center performance. Usually, machine vendors indicate the theoretical output of their

equipment in CPM (cycles or units per minute). But there are many factors that must also be considered as follows for individual machine centers before considering the effects to an integrated whole:

- Operating Efficiency or machine center "uptime": This is a measure that indicates the quantity of acceptable units produced in a production shift when it is properly supplied with in-spec components divided by the theoretical output. This should approach 100% for individual machine centers – would you accept anything less for your car? 98 to 99% efficiency is often achievable. The formula is as follows:

  E_m = Actual Machine Center Output over a given shift/(Theoretical Output or CPM * run time)

- Rejects: This is a measure of acceptable packaging production from the machine center over time. This should also approach 100%, and the allowable rate of rejection should typically be less than 1%.
- Integrated whole: The machine center cannot be viewed independently, as it is a part of the entire line.

The first thing to consider when evaluating the required performance of an individual machine center with consideration to the integrated whole is to understand that efficiencies are cumulative across machine centers in an integrated line. That is, the efficiencies of all the machine centers are multiplied together to arrive at the total line efficiency. For example, let's consider a simple packaging line made up of three machine centers.

Machine center 1 efficiency	=	90% x
Machine center 2 efficiency	=	90% x
Machine center 3 efficiency	=	90%
Line Cumulative Efficiency	=	73% (Note: Does not include downtime or run time adjustments)

Obviously, the speed range for individual machine centers must exceed the line if the throughput is to be achieved (a common error when choosing equipment). Because of the cumulative effect of inefficiencies, it is recommended to increase the machine center speeds from the most important, critical, complex, or expensive machine center in the line. Another

strategy to increase the efficiency is to add buffers or accumulators (discussed elsewhere).

The following is an example of minimizing the impact of inefficiencies, which chooses the critical machine as the benchmark for the line and increase speeds for prior and post centers (creating a pull on the filler). Often, the critical machine center is the filler. The following is an example:

Machine Center	Theoretical CPM
Component Supply	630
Filler	***600***
Capper	615
Labeler	630
Cartoner	645

When considering the integrated line as a whole, you must also factor in breaks, changeovers, and other line stoppages that that will minimize efficiency. The following is an example that illustrates this:

Example: You have been asked to design, purchase, and install a packaging line to deliver 100,000 units per shift. You have determined that you need 4 machine centers to accomplish the task in an integrated setting, with machine center number 2 being the most critical. You have decided and determined that it is possible to specify all the machine centers with an efficiency of 98% each, and maximum reject rate per machine center at no more than 0.5%. You have concluded, after factoring in breaks, maintenance, changeovers, etc. that the line will package product 7.25 out of 8 hours in a shift on average. Determine, therefore, the theoretical outputs required for each machine.

Solution:

1. Determine the accumulative effect of machine efficiencies = $E_m = (0.98)^{\wedge 4} = 0.922$
2. Determine the accumulative effect of rejects = $E_r = (1\text{-}0.005)^{\wedge 4} = 0.980$
3. Determine the overall line efficiency due to actual run time = E_L = (Actual Run Hrs/Hrs in a shift) = 7.25/8 = 0.906

4. Calculate the total efficiency of the critical machine center = $E_t = E_{m*} E_{r*} E_L$ = (0.922)(0.980)(0.906) = 0.819 or 82%.
5. Calculate then the theoretical CPM for the critical machine =

   [(Demand per shift/hours in a shift)]/(Total Efficiency) =

   (100,000/(8*60 min/hr))/(0.82) = 254 theoretical output.

   You might want to put a little "cushion" as well or safety factor to further ensure adequate delivery. So let's require the machine to deliver 280 CPM. (Obviously, you will need to determine if the vendors' equipment can produce at this rate. If not, multiple lines or machine centers in parallel may be required.)
6. Then determine the other machine center speeds, which might look something like the following:

Machine Center	Theoretical CPM
Number 1	300
Number 2	***280***
Number 3	290
Number 4	300

Also consider Qualification ranges. When Qualifying a line, do so over a range of Line Speeds to react to other equipment limitations and ensure reliable packaging at different speeds. The specifier should consider more stringent Speed requirements and Efficiencies than is planned to be Qualified. For example, a line as a whole might deliver product at 85% efficiency with a resulting production rate (throughput) of 400 to 700 units per minute (which should be verified in the Factory and Site Acceptance Test) but Qualified at (perhaps) 450 to 650 units. As well, the machine centers should be individually verified to meet their specific requirements which should be more stringent than the overall line.

As some closing thoughts on line speed and throughput, avoid the tendency to specify a greater speed than is needed or reasonably projected in the future. With higher speed often comes higher cost and complexity. Also remember to consider quality – never attempt to package a product faster than you can ensure quality product, even if it is under the possible line speed.

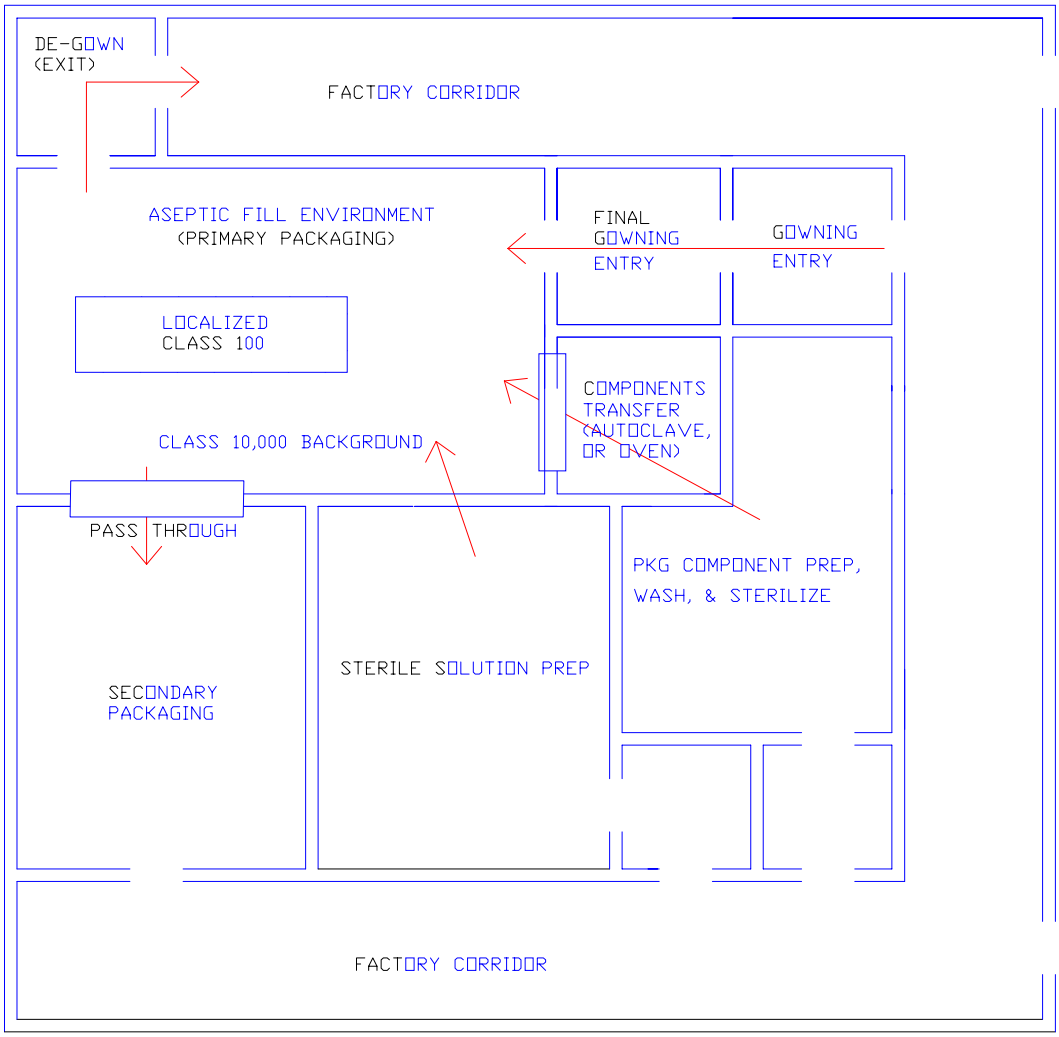
So far, we have evaluated the equipment. But what about the space in which it resides?

Space Planning

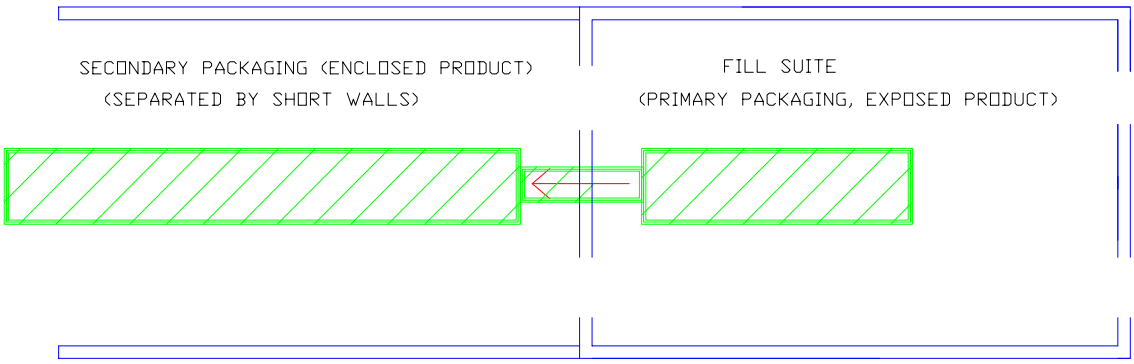
Proper space planning is essential to a successful packaging line project. The following are some considerations:

- **Adequate space:** I often instruct designers to "show skid marks of pallet lifts on the floor." It is a common problem to have crowded operations after the project is completed. This can be overcome if a robust General Arrangement is developed early. This should show the equipment, necessary clearances and accesses, pallet and other storage requirements, egress, control panels, and other "bird's eye view" of what the space will look like when actually in operation.
- **Separation:** Packaging Lines should be sufficiently separated from other lines. This separation should be physical (short walls, barriers, etc.) to keep components and pallets from become mixed up, or bottles or other items rolling from one line to the other and giving the appearance of or causing a Line Clearance failure. Sometimes, separation must be total when handling sensitive product or potent compounds, which requires even more space for walls, airlocks, and complex HVAC scenarios. Total separation is also provided (when needed) via Fill Suites at open product environments.
- **Material supply:** Another element sometimes inadequately considered is material supply, including product and components, as well as supporting items such as cleaning materials, pallets, etc.
- **Ancillary functions:** Remember to include supervisor offices, washrooms, equipment rooms, etc. needed to support the operation. As much as possible, keep utility areas separate from the finished space containing the packaging equipment. During programming for the space, make a list of all the functions needed.

The following are concept/block diagrams/drawings illustrating examples of sterile and nonsterile facilities for packaging operations (doors not shown for clarity).



TYPICAL ASEPTIC FILL/FINISH CONCEPT LAYOUT

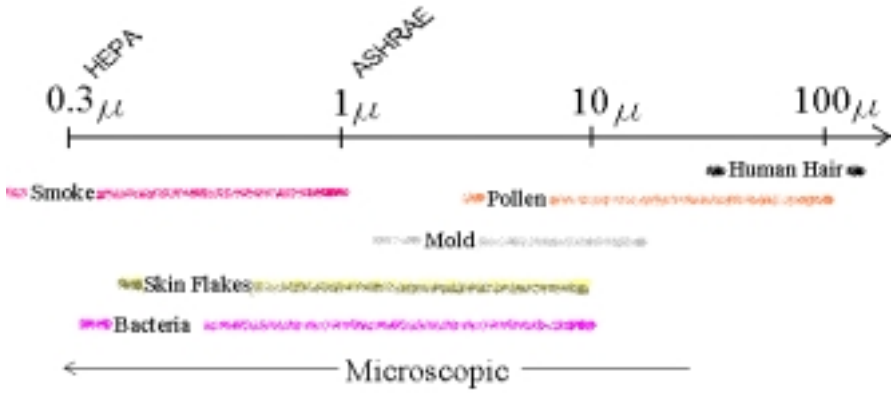


TYPICAL NON STERILE PACKAGING CONCEPT

- **Facility protection**
  - **Fill suites:** As noted previously, Fill Suites, which separate open product areas physically and environmentally, may be required for some products. Understand your product!
  - **Clean Rooms:** Some product requires classified clean rooms where it is exposed. A clean room class is measured by the quantity of viable (produced from living matter) and non-viable particles. Traditionally, classes have had such designations as 100,000, 10,000, etc. The class may be referred to as other designations by regulatory agencies (for example, the EU classifies by letters A, B, C, and D), or ISO designations. (Be aware of the EU designations since they are different for at-rest and in-operation.)

    What does the class mean quantitatively? For class 100,000, for example, there must be less than 100,000 particles of 0.5 micron and larger particles in a cubic foot of air (there are 25,400 microns in an inch, and 1,000 in a millimeter). Although the particulates may be nonviable (non-living), they still can be an "extraneous contaminate"[v] to the product, and can contaminate it biologically by acting as a microbial vehicle. Class 100,000 can be used for non-Aseptic and less critical activities. (There is no specific general clean room classification requirement for all non-sterile drugs.) However, in the direct Aseptic area (exposed sterile product) the

class must be 100, which we will discuss later. See Figure below for comparative sizes of particulate.



COMPARATIVE PARTICLE SIZES

General facility considerations

- **HVAC:** HVAC is perhaps the most complex and critical element of pharmaceutical facility design, and is beyond the scope of this course. However, one of the major considerations for packaging operations is related to the heat gain from the equipment, and acceptable temperatures, particulate level, and relative humidity. Relative humidity is sometimes overlooked, but can be critical. For example, RH over 70% begins to promote mold growth, and RH at 20% or so can cause problems with sensitive electronics and respiratory problems in people.
- **Lighting:** Lighting levels should be sufficient for the tasks. As a rule of thumb, levels between 70 and 100 fc (foot candles) should be considered where visual tasks are critical.
- **Architectural finishes**: Typical finishes suitable for pharmaceutical production are required, including non-friable and easily cleanable surfaces. Epoxy materials for wall paint and floors are common. For more sensitive products, coved corners at walls and wall/floor intersections should be considered. Also consider sloped versus level horizontal surfaces to minimize debris accumulation and facilitate cleaning.

Planning and Project Management

There are some key considerations when implementing a packaging line project. As with any project, the fundamental elements of good Project Management must be considered – Quality/Scope, Schedule, and Budget. The following are some primary elements of effective project management for Packaging Lines:

- **Specifications and Design:** See previous checklist for more specific contents of the following typical documents:
  - **URS**: The initial document of significance that defines the expectations of the equipment or the "what" is the URS (User Requirement Specification.) Here, the primary business objects are presented, with the expected performance (units/minute, efficiency, etc.)
  - **FRS**: The Functional Requirement Specification (FRS) builds on the URS, and develops the "how" of the design, with more detail and identification of specific elements. There will likely be multiple FRS', one for each machine center. Often, vendors or integrators are asked to draft the FRS. With both the URS and FRS, acquire project team approval. Ensure the end user and QA are signatories on the URS at a minimum. Sometimes, URS and FRS are combined into a single document. See previous for typical contents that should be considered.
  - **Design Spec**: The design spec will follow and contain specific information to fabricate and install the line or machine center. This usually comes from the vendor.
  - **Effective Bid packages:** Important rule – avoid "phone call engineering." This occurs when someone picks up a phone and proceeds to order a piece of equipment with little up-front documentation. I often advise, "If you don't tell the vendor in writing what you want, you probably won't be happy with what you get." Be sure to include the URS (and FRS if available) along with a Request for Quote (RFQ) that defines commercial terms, schedule, delay penalties, start-up/testing/commissioning, methods of handling changes, unit rates, etc. An early RFQ may be required if an Integrator is involved and final machine centers are not chosen. Include warrantee requirements. You also may want to consider a PM and maintenance agreement for less sophisticated Owners or for the first few years until your mechanics are well

versed in the equipment. Also request price discounts to be stated upfront along with hourly rates and perdiem caps. Consider including change parts (required to run varying products or sizes). As much as possible, specify change parts to minimize or eliminate the use of tools, and specify preset/easily identifiable adjustments. Purchase complex replacement or long-lead repair parts as part of the competitive bid. The more homework you do internally up front, the less problems and cost over-runs you'll have later.

- **Contracts:** Also include contracts for larger purchases. While each company has different limits, contracts should be considered for even semi-customized purchases over $100,000 in my opinion. Although contracts are beyond the scope of this course and the legal expertise of the instructor, the following are a few items that may need to be considered in a contract:
    - Identification of supporting documents (avoid repeating technical and most performance information as much as possible)
    - Performance guarantee (helpful in an appendix or reference documents if an "open ended" or standard contract)
        - Packaging rates of acceptable product over a set run time (may choose to perform average over three consecutive runs/shifts)
        - Reject rates
        - Schedule
    - Means of resolving conflicts
    - Commercial terms and conditions
        - Mark-ups
        - Hourly rates
        - NTE (Not to exceed) or Lump Sum costing
    - Liquidated damages, if any
    - Design/Integration deliverables
    - Requirements for subconsultants
    - Warrantee/guarantees
    - Standards
    - Patent concerns
    - Design phases and deliverables per phase

- Submittals and reviews
- Record documents
- Bidding to third parties
- Bonds, if any
- Insurance, if required
- Responsibilities for installation
- Schedule requirements (consider attaching a separate schedule that was part of the bid package)
- Start-up/Testing/Commissioning
- Qualification
- Conditions for final acceptance
- Meetings – location and frequencies
- How to handle changes
- Requirements for periodic reporting
- Financial records and reporting
- Payment terms and conditions
- Delay or penalty costs, if any
- Roles and assignments of personnel
- Intellectual Property aspects
- Software issues and back-ups
- Indemnification clauses where applicable
- Force Majeure events and implication (acts of God, national emergencies, civil unrest, war, etc.)
- Termination clauses
- Assignment of risks
- Testing required for acceptance
- Installation/construction management provisions
- Training responsibilities
- Attachments as needed to define the specific scope (Note: consider "open ended" contracts if you planning on engaging in more than one project – simply reference essential documents and the contract in Purchase Orders or other means

authorized by your legal department.)

- **Delivery methodologies:** Fit the delivery method to the project needs. Consider your company's expertise plus workload as well. The following are various considerations/methodologies:
  - **Reuse**: This involves reusing entire lines or machine centers, relocating from another facility, changing existing equipment usage, or purchasing used equipment.
  - **Self-managed**: This is where the Owner integrates the line and direct-purchases machine centers. However, this requires considerable sophistication on behalf of the Owner, is very time consuming, and transfers considerable risk to the Owner.
  - **Integrator**: This involves hiring a company to either coordinate or direct purchase machine centers and integrate as a sole-sourced package. This is an efficient method of delivering complete packaging lines with minimal resource drain from the Owner, although it can be expensive. It is recommended to assemble the line at the integrator's shop if schedule and budget permits to resolve any problems with the line prior to site acceptance. However, remember to include this in the RFQ. When bidding to integrators, have a thorough URS and design standards to ensure quality.
  - **Prime Vendor**: This involves choosing a machine center vendor to be the prime vender and integrate the entire line. Often, this involves projects where the prime vendor's machine center is predominate or multiple, and other machine centers and machine components are ancillary.
  - **Combine with A/E contract**: On large projects, some A/E (Architect Engineers) might provide equipment specifying and purchasing functions. However, be careful if it is not their primary area of expertise. If it is necessary to select this option due to resource restraints, consider requiring the A/E to sub to a qualified Integrator.
  - **Design-Build**: This could also be described as the Integrator or Prime Vendor approach, but also could include a comprehensive facility, process, and equipment Design-Build packages. This is covered in more detail in other courses, but approach this method with caution as quality issues can arise and overruns if the project is not well scoped initially.
  - **Construction Management**: This approach includes the packaging equipment under the CM agreement (the constructor). This can be an efficient method delivering

larger projects where the Owner's resources are limited, but as with DB and A/E approaches, require qualified vendors and integrators if clear expertise is not present.

- **Self-constructed**: This is when the Owner self-fabricates its own equipment. This is generally reserved for large, highly proprietary or technologically restrictive companies. Often, such approaches are limited to smaller and more specialized components, assemblies, integrative elements, or individual machine centers.

Start-up, Commissioning, and Validation

- **Setting-to-work/Start-up**: The vendors and suppliers should always place the equipment in a ready state and initially energize the equipment. Trained technicians must come to the site and debug all systems prior to turning over to the Owner for further Commissioning, Qualification, and use. If this is not properly done, considerable damage to the equipment can result.
- **SAT/FAT's:**
  - **Factory Acceptance Tests (FAT):** FAT's are a business initiative. This involves visiting the vendor's site or Integrator's shop to field test the equipment prior to shipping. This allows discrepancies and issues to be resolved ahead of time. The FAT should include similar same elements as the SAT. As much as the schedule will permit, do not allow shipping until the FAT is resolved. Before going for the FAT, acquire assurance from the vendor that they are ready. It is common to arrive for FAT testing to find they aren't sufficiently complete.
  - **Site Acceptance Tests (SAT):** SAT's are both a business and regulatory initiative. Repeat elements as necessary from the FAT, and ensure adequate inspections and testing to accept the equipment from the vendor. Once the SAT is signed off, assume it is almost yours except for warrantee items and discoveries during the IAT (if included – see below for further information on IAT's). Never pay fully until the SAT is acceptable. Also, confirm any unresolved FAT issues are concluded as part of the SAT. Remember to include SAT and FAT elements in your RFQ. Often, integrators are asked to draft and execute the SAT and FAT, or require drafting of machine center SAT/FAT's by the vendor. Remember, your staff might not have the proprietary expertise to draft a comprehensive document or execute it. However, the

Owner must be involved in the testing to be prepared for hand-off and operations. Generally, SAT's and FAT's are machine center specific. However, remember to include an integrated line SAT (and FAT if reassembled at the integrator's shop) or include as part of the Commissioning Test Plan activity. If there isn't an integrated SAT/FAT, include in your RFQ that final payments won't be made until an integrated test verifies individual machine center participation in a successful line operation.

- **Integrated Acceptance Test (IAT)**: This is a plan to challenge the line further (or as part of integrated SAT or Commissioning Test Plan) to verify the performance requirements. This is especially recommended when Integration is outsourced.

- **Commissioning and Validation**: The requirements for Commissioning and Validation are extensive, and are beyond the scope of this course (see separate courses for more coverage of this area). However, all Direct Impact elements must be Validated/Qualified if packaging drug products. Direct Impact equipment are machine centers that have a direct impact on Product Quality. Prior to Qualification, the Commissioning exercise must be thorough and robust. It must also include any aspect not included as part of the SAT or FAT, as well as verify a proper integrated line performance (Integration Acceptance Test or IAT).

  Sterile operations are even more crucial. The effectiveness of the process to produce sterile product must be verified. This is done via a process simulation utilizing media fill, or a nutrient medium that encourages microbial growth. These are repeated during the year, and must be done for each shift. Properly performed, this will result in an upper 95% confidence limit (Poisson variable), which will verify the ability of the facility/process to produce sterile product.

Closeout and Operation

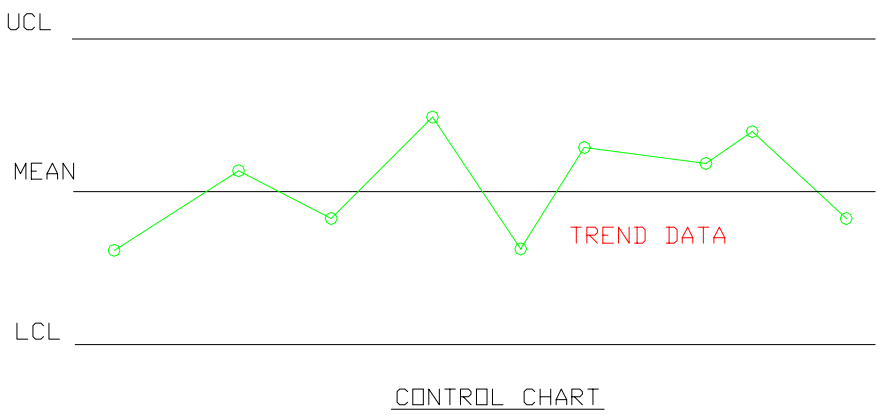
- ***Documentation:*** With any project, completion isn't successful if adequate documentation isn't turned over. This is especially true for packaging equipment. Today, equipment incorporates high technology, and Operations and Maintenance manuals as well as drawings are crucial if it is to be properly maintained and operated.
- ***Training and Qualified Workforce***: The project also is not complete until qualified staff are trained in its operation. Training should include Preventive Maintenance (PM) procedures, overview of alarms and proper reactions, safety procedures, and comprehensive operational

instructions. I recommend the Commissioning process comprehensively verify training is complete.

- ***Standard Operating Procedures (SOP):*** SOP's are essential to ensuring personnel are trained and to demonstrate compliance to regulatory authorities if challenged.
- ***Maintenance/PM's*:** As noted above, the training should include an overview of maintenance procedures. In addition, include the following:
  - *Spare parts*: Ensure spare parts that have long lead delivery are on-site or quickly available.
  - *Change parts*: As noted previously, change parts are required for multi-use lines, or for lines that run various fill volumes. These should be purchased and verified as part of the project. (Also include in the bid to keep the costs competitive).
  - *Routine Preventive Maintenance (PM):* The equipment assets should be properly logged into the CMMS (Computerized Maintenance Management System) if available, and PM's established per the manufacturer's instructions. Also, the FDA may expect to see a complete history of routine repairs as well, so remember to enter in the software all work performed on the equipment.
- ***Lifecycle management***
  - **Change Control**: Make changes to the equipment in accordance with a change control process. Equipment can easily be modified overtime in such a way compliance is not maintained, and aspects can begin to function differently than intended.
  - **TPM (Total Productive Maintenance):** Equipment and system failures add cost to an operation. Why wait until something fails? TPM includes Preventive and Predictive Maintenance. Preventive Maintenance includes intelligently performing necessary maintenance at appropriate intervals before failure occurs. As noted previously, CMMS (Computerized Maintenance Management System) is helpful in keeping track of work orders including recording and automatically issuing work orders at the appropriate time. Predictive Maintenance is performed based on gathered data (such as vibration analysis, etc.).
  - **Continuous improvement**: Operations should continue to look at ways to improve the performance and effectiveness of the Packaging Line.

As noted previously, never run a line faster than quality product can be produced. If a line is out of control, slow it down and begin to bring it up to speed in discrete increments until the problem starts to reoccur. Then, resolve the problem. A good tool for monitoring and keeping the line under control is SPC, or Statistical Process Control. SPC utilizes Control charts to organize processes into logical and manageable sizes, and visually illustrate the processes. These charts are helpful in understanding the degree of statistical process control, as well as for trending. Control charts are generally categorized in one of two types. The first is "Variable" where data is plotted in quantitative units. The second is "Attribute" where value statements are included. There are a variety of chart types within both categories.

Control Charts are plotted against three parallel lines - the mean is the centerline, the top line is UCL (Upper Control Limit) which may be two to three standard deviations above the centerline, and the lower is LCL (Lower Control Limit), also two to three standard deviations below the centerline. After the data is plotted, variations become evident. The following is an example of a Control chart:



CONTROL CHART

A methodology for continuous improvement is OEE (Operational Equipment Effectiveness). OEE focuses on improving the performance of equipment and machinery, as well as avoiding making the wrong purchases. OEE focuses on the greatest areas of improvement that will have the greatest return. The OEE can be expressed by A*B*C, where A = Availability, B = Performance Rate, and C =

Quality Rate. OEE can be used to illustrate how improvements will result in better changeovers, reliability, quality, etc. OEE can be calculated based on production rates or schedule. $OEE_{production}$ equals actual output (of acceptable quality) divided by theoretical scheduled output. $OEE_{schedule}$ equals actual process time divided by theoretical process time.

Another practical initiative is 5S. The concept behind 5S is to maintain a safe, clean, organized, and a high-performance work environment. The 5S's are:

- Sort – Eliminate anything that isn't needed
- Set in order – Organize or Simplify. Keep items in a location where they are easily retrieved and replenished.
- Shine – Keep clean
- Standardize – Develop standards for the first three S's
- Sustain – Follow the procedures

Although this seems to be common sense, many work environments are unorganized, leading to safety concerns, product mix-ups, difficulty finding items (resulting in longer cycle times), etc.

- **Calibration/PM's**: As noted above, PM's must be entered into the maintenance system. In addition, instrumentation must be calibrated, and procedures/frequencies established in the calibration system for future recalibrations.
- **Decommissioning**: After the equipment has served its useful service, a focused decommissioning exercise is needed. The equipment must be sanitized, and instrumentation calibrated to confirm state of calibration at the time of decommissioning. Also, the status in the maintenance and calibration systems must be deactivated and removed from GMP status (GMP is "Good Manufacturing Practice," signifying a state of FDA compliance.) Other documentation updates will likely be required as well.

Self-directed Assignment (Required)

Applying what you have learned from this course, choose one of the following exercises and complete: (You will be asked in the Quiz whether you completed). Expend no less than 30 minutes in this exercise.

- Take an existing packaging line for your client's operation and estimate the proper line speeds per machine center
- Given a product with which you are familiar, develop a block diagram of the required machine centers
- Choose a common product your company or client produces, or a product you routinely use. Research a filler/capper machine center(s) (internet is a good place to start) and review the required deliverables (line speed, max reject rate, materials of construction, consider the component for your type of product, etc.)

Course Summary

In this course, we have studied the fundamentals of packaging line engineering and operations for the Pharmaceutical and related applications. In the beginning, we reviewed the business and regulatory drivers and considerations for initiating a Packaging Line project. In addition, this course included an overview of packaging components, equipment machine centers, and other practical approaches for implementing a packaging engineering project. General space planning issues were discussed. Methods of determining line speed were reviewed. Finally, lifecycle considerations were discussed. For further study, other courses by the author are recommended as follows:

- ✓ K112 Fundamentals of Aseptic Pharmaceutical Engineering
- ✓ M226 Psychrometric Chart Fundamentals and its application to HVAC Troubleshooting
- ✓ P146 Commissioning Fundamentals and a Practical Approach
- ✓ P147 A Practical Approach to Pharmaceutical Commissioning and Qualification
- ✓ P160 An Introduction to Lean Six Sigma – Improving Quality, Efficiency, Profitability, and Customer Satisfaction

We welcome and request your input to the course, and how we can improve with future revisions. As well, we are interested in the types of courses you would likely take if offered.

End Notes

[i] "Volume 3 - Sterile Manufacturing Facilities," ISPE, Pharmaceutical Engineering Guides for New and Renovated Facilities

[ii] Ibid

[iii] ISPE's online glossary, http://www.ispe.org/glossary/definitionbyterm.cfm?term=Autoclave

[iv] Ibid

[v] FDA's "Guidance for Industry – Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice," dated September, 2004