

Pharmaceutical Formulation

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■ Preclinical/Preformulation Testing

Once you have discovered a new drug, it's the formulator's goal to learn as much as possible about the active portion of the drug during this early phase of development. Absorption, distribution, metabolism, and elimination (ADME) studies need to be performed on animals. You need to learn the following information about the drug before you can dose it in humans.

- *Absorption.* The following factors can influence drug absorption:
 - *Solubility.* Knowing the drug's solubility over a wide pH range is paramount. FIGURE 2-1 shows a simplified diagram of the digestive tract.
 - *Partition coefficient.* This is a measure of the active's lipophilicity, which indicates its ability to cross cell membranes. Because human cells are constructed of phospholipid bilayers, lipophilicity contributes to the drug's rate and extent of absorption.
 - *Permeability.* This is the measure of a drug's passive diffusion through the intestinal wall. The higher the permeability, the greater the drug's absorption will be.
- *Distribution.* Solubility and lipophilicity also play a major role in drug distribution as described previously.
- *Protein binding.* Drugs can bind to proteins, mainly albumin, based on acidity or basic properties. If a drug is highly bound, its half-life can be greatly increased because the bound drug cannot permeate into body issues and be metabolized and eliminated.
- *Metabolism.* The liver is the main organ involved in drug metabolism. Metabolism is the conversion of a drug from a lipid-soluble form to a more water-soluble form so that it can be eliminated. A long list of enzymes can metabolize a drug by chemical reduction, oxidation, or hydrolysis. Cytochrome P450 plays a major role in this process.
- *Excretion.* Excretion can occur through the following pathways:

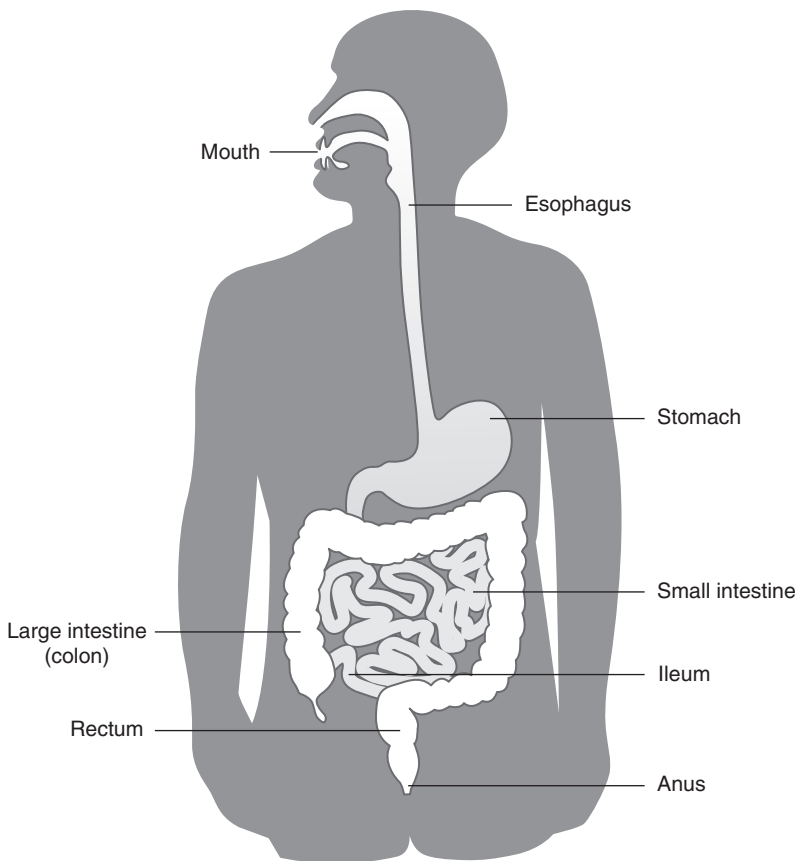


FIGURE 2-1 Anatomy of the digestive tract.

- *Kidneys.* Once a drug is metabolized to a more water-soluble form, it can be excreted by the kidneys. The pH of the urine can affect the rate of excretion through the kidneys. Intentional acidification of the urine can promote the excretion of toxins and unwanted drugs.
- *Bile.* Some drugs pass through the liver unchanged and can be excreted in bile.

Toxicity studies can be performed on mice, rats, dogs, or even monkeys to ensure safety before introduction in to humans.

Once the drug passes the 6 to 7 pH of the mouth, pH of the digestive system decreases as it enters the stomach. The stomach's pH is typically 1 to 5 (1–2 in the fasting state and 2–5 in the fed state). The pH then increases through the small intestine, which usually ranges in pH between 5 and 7. The digestive tract terminates at a pH of about 5.5 to 8 in the colon. The drug's solubility range allows you to know where it will dissolve in the intestinal tract and thus when it will be absorbed.

The dissociation constant (pK_a) is the measure of the amount of drug that is non-ionized at a given pH. A drug needs to be neutral/nonionized to be absorbed in the digestive tract. You can predict absorption and the area of absorption based on the pK_a value.

Drug stability is tested through forced degradation studies. Subjecting the drug to various conditions can predict future interactions. Typical stressing agents include, but are not limited to, heat, acid, base, peroxide, and light.

■ Dosage Form Design: Choosing a Dosage Form

The first step in dosage form design is to determine the drug's site of absorption. For drugs that are intended to be absorbed systemically, the dosage form needs to dissolve in the mouth, stomach, or intestines. Some absorption occurs in the buccal (oral) cavity (mouth) of very soluble actives. This site is usually reserved for conditions that require rapid onset of relief such as migraine headaches. Very little absorption, if any, occurs in the stomach. That leaves the intestines as the main site for drug absorption.

Some drugs can irritate the stomach or degrade at a pH between 2 and 3. It is advantageous to protect such drugs during passage into the small intestine. If the drug is meant to exert its action in the colon, the dosage form has to remain intact until it enters the colon. This can be achieved by coating the dosage form with an enteric coating that dissolves at a pH between 5.5 and 7, which is typical of the colon.

The second step is to determine the drug's dosing interval based on the half-life of the drug. The half-life is the amount of time needed for half of the dose to be metabolized and eliminated. A relatively short half-life may require dosing 3 or 4 times a day whereas a longer half-life may require only 1 or 2 doses per day.

Several options are available when introducing a drug product into the body via the oral route of administration:

- *Tablets:*
 - *Orally disintegrating (ODTs) and sublingual.* These tablets dissolve in the mouth, making the drug available for absorption in the buccal cavity or farther down the digestive tract.
 - *Immediate release (IR).* These tablets dissolve in the stomach for immediate absorption.
 - *Modified release (MR).* These tablets dissolve slowly to delay or prolong drug absorption.
 - *Effervescent.* These tablets liberate CO_2 and yield oral solutions for quick absorption.

- *Capsules:*
 - *Hard shelled.* Typically made of gelatin, these capsules can also be made of hypromellose (formally known as hydroxypropyl methylcellulose). Hard capsules can be filled with liquids, powders, granules, mini-tablets, or any combination of the last three.
 - *Soft gelatin.* Active is introduced as a solution or suspension between two ribbons of soft gelatin and sealed to form a soft gel.
- *Powders or granules:*
 - *Powders for oral suspension (POS).* Powders are stored in dry form for reconstitution prior to dispensing.
 - *Powder packets.* Powder is stored in small pouches or sachets for administration in dry form or for suspension or solution prior to administration.
- *Liquids:*
 - *Oral solutions.* Active is in solution for quick absorption.
 - *Suspensions.* Active is in solid form suspended in a liquid vehicle.

Formulation Basics

For the sake of this text, we concentrate on solid dosage forms. More specifically, we focus on the most prevalent dosage forms: tablets and capsules. There are three basic ways to make tablets and capsules:

- Direct blend
- Wet granulation
- Dry granulation/roller compaction

Deciding on one of these techniques depends on some basic information regarding the active you want to deliver:

1. *Is the active compressible by itself?* Simply try to compress the material using a hand press and a set of tablet tooling. If a compact is formed, the active is at least somewhat compressible. In this situation, you can try a direct compression process. Mix this active with other compressible excipients (inactive ingredients) and compress into tablets. Microcrystalline cellulose, lactose, and dibasic calcium phosphate come in compressible grades that form tablets nicely. If the active is not compressible and is not sensitive to moisture, then a wet granulation technique can be employed. In wet granulation, the active, alone or with other excipients, is mixed with water and energy is exerted on the materials to

create granules through agglomeration. If the active is not self-binding, a binder such as povidone or hypromellose can be added to the formulation to aid in granule formation. Once the granules are formed, the moisture is removed to yield a more compressible powder.

2. *Does the active flow by itself?* A vast majority of actives do not flow by themselves. For compressible actives that do not flow well, you need to choose an excipient to increase flow. A glidant, such as colloidal silicon dioxide, can help ensure that the final blend adequately flows into the tableting or encapsulation machine. If the active does not flow or compress well, a wet granulation route should be used.
3. *Is the active moisture sensitive?* If the drug degrades in the presence of water or other solvents, a direct blend technique is desired. If the active is both moisture sensitive and is poorly compressible, a roller compaction method can be used. During roller compaction, also known as dry granulation, the active is mixed with excipients and is passed between two compression rolls to form a “compact” or “ribbon.” The resulting compact is passed through a mill to reduce its particle size to optimize flow and uniformity. This process makes the material denser and changes its surface structure to promote compression into a tablet or filling into a capsule.
4. *What percentage is the active of the final dosage form weight?* Direct blending is best suited for actives that are present in quantities of approximately 25% or more. For actives present at less than 25%, wet granulation is desired to ensure homogeneity. Even though it is not preferred for low-dose actives, direct compression can be used if the drug is moisture sensitive. In this case, special care needs to be taken to choose ingredients of the correct particle size, shape, and density. This will ensure that the drug is equally distributed, or homogeneous, throughout the blend, which will result in the correct dose being delivered to the patient.
5. *Is the drug sensitive to compression forces?* If the act of compression causes degradation or changes its physical or chemical form, direct blending is the desired process followed by encapsulation instead of tablet compression.
6. *Does the resulting tablet or capsule disintegrate in water?* If the disintegration time of the immediate release (IR) product is excessive, addition of a disintegrant, such as croscarmellose sodium or sodium starch glycolate, can speed the breakup of your dosage form. Disintegrants swell when contacted with water, thus helping to rupture the tablet or capsule.

Before employing one of the techniques described, it is advantageous to check compatibility of your active with various materials that you may want to use to obtain your final dosage form. Compatibility studies (sometimes called binary studies) can be performed at room temperature or at accelerated temperature and/or humidity. Because some interactions do not present themselves at room temperature, high temperature

and humidity are recommended. Simply mix your active with potential inactive ingredients to identify possible interactions that may lead to degradation of the active. Pick a ratio that will best represent your final dosage form. For example, magnesium stearate, a lubricant, and colloidal silicon dioxide, a glidant, both contain basic functional groups and can cause degradation of some actives. Compression of the binary mixtures on a hand press can get the ingredients in intimate contact and further simulate the final dosage form.

Problem Formulations

Because drug absorption depends greatly on water solubility, poorly soluble actives pose a huge challenge for formulators. The following subsection describe some basic solutions to overcome solubility issues.

Particle Size Reduction

Reducing the active's particle size increases the surface area of the active to promote dissolution. This can be achieved by milling or grinding. The extent of particle size reduction depends on the degree of solubility of the active. For minor solubility issues, simple milling will suffice. Reducing the active particle size from 1000 μm (microns) down to 200–500 μm can have a profound impact on dissolution of your active.

For extreme cases, micronization may be necessary. Micronization is typically considered to be reduction of particle size down to below 10 μm . This increases the surface area exponentially. In extreme cases, particle size reduction can even be taken a step farther down to the submicron or nanometer range.

Addition of a Surfactant

Addition of a surfactant, such as sodium lauryl sulfate (SLS), can promote dissolution of a poorly soluble active. A surfactant works by reducing the surface tension between the active and the surrounding fluid. This allows for increased wetting of the solid, which increases dissolution of the drug.

Creation of a Solid or Molecular Dispersion

Dispersions can significantly increase the solubility of your drug. A solid dispersion is formed when a poorly soluble crystalline active is dissolved along with a stabilizing polymer such as hypromellose or povidone. The mixture is then dried, and the resulting material is more soluble than the starting active. This is possible because the active is converted from a highly ordered crystalline form to a random amorphous form. This amorphous form has a higher energy state, resulting in rapid drug dissolution.

Degradation Issues

The most common type of degradation is hydrolysis. Some drugs may break down when contacted with water. Silica-based or clay-based desiccant systems can adsorb

excess moisture and protect the dosage form against hydrolysis. Molecular sieves are stronger adsorbers that can be used in the case of extremely moisture sensitive drugs.

Some drugs, such as mesalamine, are sensitive to oxygen. Steps to protect this molecule from oxygen must be employed. Simple antioxidants, such as ascorbic acid and tocopherol (vitamin E), can be used to slow or reduce/eliminate the oxidation process. Special packaging can be employed to minimize the effects of oxygen as well. Oxygen scavenger packets can be placed in the bottle to sequester residual oxygen once the bottle is sealed. In the most extreme cases, the head space (empty space) in a bottle can be purged with nitrogen to displace the oxygen before the container is sealed.

■ Stability Testing

Once you have a formulation that shows some promise, you must check whether it will remain consistent over time. Chemical, as well as physical, changes can occur when an active is put in intimate contact with fillers, binders, lubricants, capsule shells, and so forth. Capsule contents can form a hard plug over time if any of the components are hygroscopic. Binders, such as hypromellose and povidone, can absorb moisture when exposed to excessive humidity. Starch, which can be used as a binder and a disintegrant, is hygroscopic and will absorb water. Empty capsule shells themselves can contain up to 16% water that can contribute to this phenomenon.

Some excipients, such as polyethylene glycol (PEG), have been proven to cause cross-linking with gelatin to delay release of drugs in capsule form. Because gelatin can be used as a binder, cross-linking, even though less common, can occur in tablets as well. Tablet formulations that contain sugar can harden over time, delaying drug release.

When testing stability of your product, the International Conference on Harmonisation (ICH) recommends testing pharmaceutical dosage forms at the following room temperature and accelerated conditions:

- 40/75—40°C and 75% relative humidity (RH)
- 30/60—30°C and 60% RH
- 25/60—25°C and 60% RH (controlled room temperature)

The final product needs to be tested after 4, 8, and 12 weeks at 40/75. Product is also placed at 30/60 as a backup in case the 40/75 data are unacceptable. If the product is acceptable after 12 weeks at 40°C and 75% RH, it is assumed that the product should be stable for 2 years at controlled room temperature. You must back this up with actual testing for 2 years at controlled room temperature.

Some simple tests can be employed to monitor physical changes that may indicate a stability problem:

- *Tablet or capsule weight.* An increase in the weight of a dosage form can indicate moisture absorption. Excessive water uptake can lead to stability issues for your

active if degradation is hydrolysis driven. A loss in weight can reveal that maybe too much desiccant is being used in the packaging.

- *Change in appearance and feel.* Discoloration (ie, speckles) can indicate degradation of your active and possible interaction between ingredients. If the color of an active “bleeds through” the coating, more coating may be required or a physical change in the active has occurred. Tackiness can indicate a problem with active melting or coating issues.

Some of these changes can alter drug release:

- *Tablet hardness.* A decrease in tablet hardness can indicate a physical change and interaction between the ingredients that can lead to a change in drug dissolution. Softening of a tablet or capsule can show excessive water uptake, active sublimation, or formation of a eutectic mixture. An increase in tablet hardness can lead to an increase in disintegration time.
- *Disintegration.* The time it takes for a tablet to disintegrate can let you know if the tablet is changing over time. An increase in disintegration time can slow down the drug’s dissolution, which in turn can delay absorption.

Pilot Batches

After a formulator/formulation scientist has developed a laboratory scale product and/or process, the next step toward commercialization is to scale it up in a pilot plant setting. The purpose of pilot batches is to confirm that the data, information, and observations obtained for smaller laboratory bench-top scale batches are reproducible in larger pilot scale manufacturing. Because not all formulations/processes behave the same at all manufacturing scales, one of the other main objectives of pilot plant manufacturing is to define any changes to the formulation or process that must be made when the product is produced on a larger scale. Laboratory scale batches are typically on the order of 1 to 5 kg in batch size, whereas pilot scale batches typically range from about 10 to 100 kg in batch size, depending on the working capacity of the pilot plant equipment.

Solid dosage forms (tablets), which are the most predominant form of pharmaceutical products, are discussed in this section along with the issues attached to scale-up processing. Typically, other dosage forms such as liquids (solutions or suspensions) have inherently fewer scale-up problems. Pharmaceutical processes involved in solid dosage form manufacturing of tablets generally fall into two distinct categories:

1. Granulated products
2. Directly compressible products

Granulated products are traditionally manufactured using a series of equipment pieces also known as the equipment train. For granulated products, the following is a typical equipment train used for tablet processing:

- Granulator (high shear, low shear, top spray)
- Dryer (fluid bed or tray drying)
- Milling (oscillating, impact, or conical)
- Blending (twin shell blending or tote/bin blending)
- Compression (rotary tablet press)
- Tablet coating (film or sugar)

The main advantage of granulating products is that a more consistent product is produced and it is easy to incorporate materials whether they are active ingredients or functional excipients. The main disadvantage of granulated products is the increased cost in capital equipment because they generally are more complex to produce as a result of a long equipment train. This complex train of equipment also leads to an increase in the time it takes to manufacture because these types of products require an increased process complexity. One must consider material movement between pieces of equipment in the train and how this will be handled (manually or by some form of mechanical transfer). Bearing in mind how the product will be handled on a larger manufacturing scale, it may be prudent to evaluate the effect of mechanical material transfer, if it is feasible in each specific pilot plant setting.

For direct compression products, the following is a typical equipment train used for processing:

- Blending (twin shell blending, tote/bin blending, or sigma/ribbon blade mixing)
- Compression (rotary tablet press)
- Tablet coating (film or sugar)

The main advantage of direct compression products is that they are relatively easy to produce because of a straightforward manufacturing process/equipment train, which generally provides a reduction in the overall processing time. The disadvantage of this type of process is that the product quality and reproducibility are much more dependent on the raw material. Therefore, it is essential that the raw material vendors provide consistent raw materials that meet your specifications. If the raw material specifications are not set appropriately, this can lead to processing problems or finished product testing issues such as segregation. As the raw materials push the high and low ends of the specification, this may yield product failures as the ability to process the raw materials is diminished.

There are other types of niche pharmaceutical dosage forms that utilize unique types of processing equipment required for their specific dosage form requirements, such as these:

- Liquids (solutions and suspensions)
- Hard-boiled “candy” lozenges
- Transdermal patches
- Dermatologic (creams, gels, ointments, solutions, or shampoos)

- Suppositories
- Injectable sterile products
- Quick/fast-melting wafers
- Continuous processes (reserved for very large scale products)
- Film casting

Because these dosage forms are not the most prevalent in the United States, this discussion focuses on tablets, the most commonly utilized dosage form. For most large pharmaceutical companies, tablet production is the most prevalent dosage form produced.

For existing types of manufacturing equipment, there is no issue with finding equipment that is utilized for traditional pharmaceutical solid dose processing. It should be noted that when going from the equipment you have in the laboratory to that available in your specific pilot plant, there may be differences with respect to equipment design and specifications for each individual type of process. For example:

- *High-shear granulation.* Change in configuration (top driven or bottom driven), size, number and placement of chopper blades, configuration of mixing or impeller blade, or the tip speed of blade
- *Tray drying.* Volume of air, size, number and area of trays, drying temperatures
- *Fluid bed drying.* Bed height, volume of air, drying temperatures
- *Milling.* Types of mill, oscillating, conical, air, jet
- *Blending.* Blender size, shape, configuration, use of extended blender leg
- *Tablet compression.* Turret speed, dwell time, feed frame speed, gravity or force fed feeders, pre- and main compression capabilities, insertion depth, use of tapered dies, use of coated tooling
- *Tablet coating.* Air volume, pattern and atomization spray settings, spray rate, type of spray nozzle
- *Facility.* Ability to condition incoming air, mechanical material transfer

To scale up processing in a pilot plant, strive to use equipment of similar design at both laboratory and pilot scale so as to minimize variables that could lead to non-reproducible results.

However, for new or novel dosage forms, or other processes done at laboratory scale, similar or identical pieces of pilot scale available may not be available. In some cases, the process may be so unique or innovative that pilot plant (and larger scale) equipment does not yet exist or is not readily available for purchase without significant customization. In these types of cases, it is necessary to work with a process equipment manufacturer to design and develop or configure a suitable piece of manufacturing equipment that meets the requirements set forth by the development formulation scientists and process engineers. Although working with existing pharmaceutical equipment manufacturers is helpful because they are familiar with CGMPs, be sure not to overlook the opportunities available in other manufacturing disciplines for equipment that may have similar manufacturing attributes. Food manufacturing has a great deal

of similarity to pharmaceutical processing because both utilize powders as a predominant base material.

As a generalization, pilot batches should intentionally be approximately one-tenth the scale used for commercial manufacturing scale. When scaling up to pilot scale there may be subtle or significant differences with respect to the type and design and manufacturer of the process equipment. There may even be differences within a specific manufacturer's line for equipment as the scale of the equipment increases in size.

One consideration that should be made at the start of pilot scale work is the processing time. This should be taken into consideration because the eventual intention is to manufacture at a commercial plant and the processing time has a significant impact on the operational efficiency of manufacturing plants. Although the goal should be to make a very robust formulation/process, if it comes at the expense of an extended processing time, the manufacturing plant or contractor may reject the process. Or it may get translated into higher labor costs for the production. Processes that are overly complex or lengthy will decrease the plants' operating efficiency and ability to manufacture other products because most processing equipment throughout the plant is shared with other products/processes. Reasonable attempts should be made to keep processing times and equipment utilization to a minimum when developing a process.

It is very likely that a process developed at smaller laboratory scale by the formulation scientist may undergo significant changes to the formulation or process at pilot scale. If the project does not already have a process engineer assigned to it (either from R&D or from the manufacturing plant), this is an ideal time to bring one into the project team. The process engineer can bring some helpful insights that the formulation scientist may not be aware of, such as follows:

- Availability of pilot plant and manufacturing plant equipment
- Design and process capabilities of pilot plant or manufacturing plant equipment
- Familiarity with various or similar types of processes

The availability of materials, especially new chemical entities (NCEs), are generally very limited because they are made in small chemical synthesis batches and are expensive to produce. Depending on the NCE, there may only be hundreds of grams or a few kilograms of material available for use. In this case, experimentation may be limited and a well-planned experimental design must be designed to conserve material. Contrary to this, the development of many over-the-counter (OTC) medicines are relatively inexpensive when compared to NCEs and the cost will not generally figure in largely to the experimental plan, so a more thorough evaluation is more easily obtained.

■ Granulation

The formulator and/or process engineer should be prepared to make alterations to the process based on findings that occur during this experimental pilot plant phase. There

are some well-documented areas where adjustments are typically required to reproduce results found at smaller scale. In the area of high shear granulation, changes typically made at pilot scale include the amount of granulating fluid required to achieve the desired granulation endpoint. This can be a somewhat dramatic change. An increase in batch size by 10 times (5-kg lab scale to 50-kg pilot scale) will generally require a significant reduction in the amount of granulation fluid used. This reduction may be on the order of 10–20% or more. This is due to increased efficiency of the manufacturing equipment at the larger scale and the overall bed height.

This generalization may not hold true for all materials or formulations and some formulations may actually require more granulating fluid to achieve a suitable granulation. The same reductions will generally apply when increasing from pilot scale to full-scale manufacturing. The granulation endpoint will eventually be based on some type of measurement (such as power draw, kW). However, some smaller pieces of equipment may not have suitable meters, so this scale may be the first opportunity a scientist has to measure the impact of changes made on the formulation/process. Consequently, a large part of the determination of the granulation endpoint may be based on visual and tactile cues. It is prudent at this stage to also stress the process to see where the limits lie and how robust the process is. It is a lot easier, faster, and less costly to do this experimentation at pilot scale rather than at larger manufacturing scale.

Drying

Drying of a granulation may or may not see significant changes. The most notable area will be the drying time, which is predominantly a function of the amount of air flow the dryer is capable of handling. The drying time is directly related to the volume of air flow, so this will be the parameter with the most impact on the process. Also, seasonal changes in processing air humidity for unconditioned air should be taken into account. Depending on the robustness of the formulation, one may see an increase in the fine material produced during processing. This increase may be caused by increased attrition within the fluid bed dryer resulting from greater product movement.

If the granules produced during granulation are not robust enough, particles may wear off or break to generate material of a smaller particle size. This is not an issue if tray drying is used. Tray dryers may be used at this scale; however, when the product is moved to larger scale manufacturing, it is not typical to use tray dryers because of the lengthy time of drying cycles. It is recommended to try and mimic the equipment used at larger scale to evaluate any changes. It is also important to check on the air handling of the equipment to note if the specific unit has capabilities for the treatment of incoming air. Air that has been pretreated (dehumidified) will have more drying capability than untreated (unconditioned/ambient) air and will affect the processing time.

Milling

Milling operations may significantly affect the scale-up process. Different types of mills have significantly different attrition and may result in significantly different particle size distributions. Other factors include the screen sizes available. Sometimes those available at pilot scale may differ slightly from those used at smaller lab scale. Factors such as mill speed need to be taken into account and may impart more attrition at higher mill speeds. It is important to try and match the mill type, mill screen size, and mill speed that you intend to use at production scale.

Blending

Blending operations are a bit more predictive. There have been significant studies done to determine the appropriate changes required to scale up a blending process for units configured as a V-blender. Because the material moves a somewhat consistent distance during the rotation of the blender, the distance particles travel is easily calculated and based on the size of the blender, so one can calculate an approximate blending time. This should be confirmed by utilizing blend optimization where batches are blended at lower and higher than anticipated blending times.

Confirmation of the data is best done by taking blend samples (typically, 1–3 times the finished dosage unit). Replicates are also easily taken at the same time should a retest of the blend sample be required. The predominant type of blend sampling is done via thief sampling, which intrinsically creates problems by trying to achieve a “static” sample from within a powder bed. Blend sampling results are also affected by static charge of materials and the ability of material to flow into the sampling cavity. Whenever possible, blend sampling should be limited to only one operator to minimize any variations caused by sampling error. Blend sampling should be designed to try and simulate the most difficult blending situations, such as sampling areas near dead spots or near the axis of rotation.

Scale-Up

After a scientist (formulation scientist, process engineer, or both) has developed a pilot plant scale product/process, the next step toward commercialization of the product/process is to scale it up in a full-scale manufacturing plant. The purpose of scale-up batches is to confirm that the data, information, and observances obtained at smaller pilot plant scale is reproducible at full-scale manufacturing and to define any changes that need to be made at this larger scale.

Typically, scale-up batches are initially done as “feasibility” or experimental batches. Feasibility trials can be performed as a single batch to confirm that the process scale-up goes as expected and there are no unexpected surprises at this phase. However, it is usually prudent to plan to have enough raw materials and plant time allocation to

make additional batches should processing parameters need to be altered or should the scientist wish to make additional batches to see if the process is reproducible. Feasibility batches may or may not be done at full manufacturing scale.

The cost of the active ingredient and the raw materials affect the size and number of batches to be made at this scale. One factor that also plays a role is the manufacturing schedule of the plant or contractor where manufacturing will take place. If equipment needed for the feasibility trial is in the part of a plant that is heavily in demand for other products/processes, it may be difficult to gain access to that area because the plant will need to displace its current marketed products to accommodate the plant trial. These types of feasibility trials are often used for experimental purposes only because there are usually changes required within the process that need to be further explored.

Raw materials or active ingredients utilized at this stage often do not require full characterization or testing to be used for these types of large-scale experiments. These factors will usually limit feasibility batches being used for purely “experimental” work rather than for human consumption, registration, or clinical trials.

If the active ingredient being used in your product is new to a manufacturing facility, you may be required to perform a cleaning validation of the active ingredient. The purpose of this is to prove that after manufacturing products using this active ingredient is completed, the carryover of material is lower than the permissible levels.

Some limits that have been mentioned by industry representatives in the literature or in presentations include analytical detection levels such as 10 ppm, biological activity levels such as 1/1000 of the normal therapeutic dose, and organoleptic levels such as no visible residue or odor residue (when using flavors in the process).

There are many factors that affect the success of a feasibility trial:

- Similarity in design of the equipment that was used during the laboratory and pilot plant phases of development
- Changes required in the process
- Fluid volume required for granulation
- Granulation drying time
- Size of milling screens
- Mixing/blending times
- Changes in tablet press tooling

After a feasibility trial is successfully completed (and any corresponding changes made to the formulation and/or process), a qualification trial is often required. A qualification trial serves to reproduce the findings, data, and observations seen during feasibility batches. Material produced at this stage generally has more refined specifications for materials and testing requirements are significantly more than those for feasibility batches. As a result, material produced during these types of trials may be used for

human use or clinical trials if the batches are produced under Good Manufacturing Practice (GMP) conditions.

Several technical transfer issues may arise during these trials that may require some changes to be made. One area to pay special attention to is material transfer. Typically, at laboratory and pilot scales, material transfers are done by hand. However, at large scale the volume of material is usually too large to move manually and technology is utilized to facilitate the manufacturing process. You may see the use of drum lifters, drum inverters, screw feeders, vibratory hoppers, or vacuum transfer units. The use of vacuum transfer units can be especially problematic if you have a material that has a tendency to segregate. This is possible with materials that have wide particle size distributions or with materials that have a two or more peaks in their particle size distribution. The use of any vibratory system during the process may induce a percolation effect where smaller particles are driven down in between larger particles, causing the powder bed to segregate. Visually this will be seen by looking at the top of the powder bed, and you will see what visually appear to be the larger particles rising to the top of the powder bed.

Overages of materials may also be needed at this stage because the type of material transfer is quite different from that used at smaller scales. As a result, some of the processes used for material transfer may cause selective material loss. To compensate for this an overage may be added with sufficient justification to determine the appropriate overage needed for your specific process. Overages should not be added without specific justification. CGMPs require that formulations are formulated to 100% of label claim.

Process Validation

Process validation principles that are described here are applicable to any drug product that is administered to either humans or animals. A process validation guideline can be found in Section 10.90 (21 CFR 10.90). Process validation is a required part of current good manufacturing practices (CGMPs) for pharmaceuticals. These requirements can be located in 21 CFR, specifically in Parts 210 and 211. We discuss process validation aspects and the concepts that are a significant part of a validation program. Specific requirements of process validation vary depending on such factors as the nature of the specific product (such as dosage form) and the nature of the specific process (granulation, direct compression, liquid manufacturing, etc.).

It is important to understand some of the basic terminology used within the process validation field. Following are some of the most commonly used terms relating to process validation:

- *Installation qualification.* An equipment trial that establishes confidence that the processing equipment is capable of consistently operating within the established

limits and tolerances. This step is typically performed when new equipment is installed to adequately prove that it is suitable for its intended use or purpose. This is normally performed by the site where the equipment is being installed.

- *Process performance qualification.* A processing trial that establishes confidence that the process is effective and is reproducible.
- *Performance qualification.* A process trial that establishes confidence that the finished product produced by a specific process meets the testing requirements for its intended use.
- *Prospective validation.* A process validation trial conducted before a new product is released for its intended use to establish that the predetermined results can be achieved on a consistent basis. Typically, this is performed on three consecutive batches.
- *Validation.* Establishing documented evidence that a specific process will consistently produce a product meeting its predetermined specifications and quality.
- *Validation protocol.* A definitive written plan that describes how the validation will be performed, including the test criteria, sampling intervals and requirements, product characteristics, production equipment, and acceptable limits for test results.
- *Stressed or worst-case conditions.* A set of conditions encompassing the high and low extremes of the processing limits that pose the greatest chance of process or product failure. Such conditions may or may not induce product or process failure.

General Concepts

Assurance of product quality is derived from careful attention to a number of factors including selection of quality parts, equipment, and materials; adequate product and process design; control of the process; and in-process and end-product testing. Because of the complexity of the products, routine finished product testing alone often is not sufficient to ensure product quality. Some finished product tests have limited sensitivity. In some cases, destructive testing would be required to show that the manufacturing process was adequate, and in other situations finished product testing does not reveal all variations that may occur in the product.

The basic principles of quality assurance have as their goal the production of articles that are fit for their intended use. These principles are defined in the following statements:

- Quality, safety, and effectiveness must be designed and built into the product.
- Quality cannot be inspected or tested into the finished product.
- Each step of the manufacturing process must be controlled in a way to maximize the probability that the finished product meets all quality and design specifications.

Process validation is a key element in ensuring that these quality assurance goals are met. It is through careful design and validation of both the process and process controls that the manufactured products that are produced in consecutive lots meet the predetermined acceptable criteria.

The FDA defines process validation as follows:

Process validation is establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality characteristics.

It is required that a written validation protocol is approved prior to commencing any validation batch manufacturing. This protocol specifies the manufacturing procedures, the required testing/sampling intervals, and specifically identifies the locations to be tested and what testing data will be collected. A protocol should specify the required number of repeated process runs (typically three consecutively) to prove that the process is reproducible. The test conditions for these runs should encompass stressed conditions at the upper and lower process limits, which possess the potential to create a process or product failure. The process validation documentation should include information on the suitability of materials and the performance and reliability of equipment and systems.

Key process variables should be monitored and documented. Analysis of the data collected from monitoring will establish the variability of process parameters for individual runs and will establish whether or not the equipment and process controls are adequate to ensure that product specifications are consistently met.

Finished product and in-process test data can be of value in process validation, particularly in those situations where quality attributes and process variability can be readily measured. Where finished (or in-process) testing cannot adequately measure certain attributes, process validation should be derived primarily from qualification of each system used in production and from consideration of the interaction of the various systems.

CGMP Regulations for Finished Pharmaceuticals (The Current Codified CGMP Regulations, CFR Parts 210 and 211)

Section 211.100—*Written procedures; deviations*—which states, in part: A requirement for process validation is set forth in general terms:

There shall be written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess.

Several sections of the CGMP regulations state validation requirements in more specific terms. An excerpt from a section is as follows:

Section 211.110, *Sampling and testing of in-process materials and drug products.*

(a) Control procedures shall be established to monitor the output and validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product.

Preliminary Considerations

A manufacturer should evaluate the factors that affect product quality when designing and undertaking a process validation study. These factors may vary considerably among different products and manufacturing technologies and could include, for example, component specifications, air and water handling systems, environmental controls, equipment functions, and process control operations. No single approach to process validation will be appropriate and complete in all cases; however, the following quality activities should be undertaken in most situations.

During the research and development (R&D) phase, the desired product should be carefully defined in terms of its characteristics, such as physical, chemical, and performance characteristics. It is important to translate these product characteristics into meaningful specifications that will serve as a basis for description and control of the product.

Documentation of changes made during development will provide traceability that can later be used to pinpoint solutions to future problems.

The product's end use should be a determining factor in the development of product (and component) characteristics and specifications. All pertinent aspects of the product that have an impact on safety and effectiveness should be considered. These aspects include performance, reliability, and stability. Acceptable ranges or limits should be established for each characteristic to set up allowable variations. These ranges should be expressed in measurable terms.

The validity of acceptance specifications should be verified through testing and challenge of the product on a sound scientific basis during the lab scale, pilot plant scale development, and production phase.

Elements of Process Validation

Prospective Process Validation

Prospective process validation includes those considerations that are made before a new product is introduced or launched or when there is a significant change in the manufacturing process that may affect the product's characteristics, such as uniformity or identity. The following are considered as key areas of prospective process validation.

- *Equipment and process.* The equipment and process should be designed and/or selected so that product specifications are consistently achieved.
- *Equipment installation qualification.* Installation qualification identifies that the various pieces of processing equipment are capable of consistently operating within established limits and tolerances.

After process equipment is designed (using design qualification), it should be verified that it is capable of operating satisfactorily within the operating limits required

by the process. This portion of validation includes examination of the equipment design, determination of equipment calibration, equipment maintenance, adjustment requirements, and identification of critical equipment features that could potentially affect the process or the product. Any information gathered from these qualification studies should be used to establish written procedures covering equipment calibration, maintenance, monitoring, and controls.

When assessing the suitability of a specific piece of processing equipment, it is insufficient to rely entirely on the manufacturer's representations or specifications. Practical engineering principles should be the first step in the equipment suitability assessment. It is important that equipment qualification simulate actual production conditions, including those that are worst-case situations.

Equipment tests and challenges should be repeated several times to ensure reliable, accurate, and reproducible results. All acceptance criteria must be met during the test or challenge. If any of the tests performed show that the equipment does not perform within its specifications, an investigation should be performed to identify the root cause of the test failure. Corrections should be made where appropriate and additional testing runs performed to adequately verify that the equipment performance is within the stated specifications. Variability of the equipment that is seen between and within runs can be used as a selection criteria basis for determining the number of testing trials required for the subsequent performance qualification studies.

Once the equipment configuration and performance characteristics are established and qualified, they should be documented. The installation qualification should include a review of pertinent maintenance procedures, repair parts lists, and calibration methods for each piece of equipment. The objective is to ensure that all repairs can be performed in such a way that will not affect the characteristics of material processed after the repair. In addition, special postrepair cleaning and calibration requirements should be developed to prevent inadvertent manufacture of a nonconforming product. Planning during the qualification phase can prevent confusion during emergency repairs that could lead to use of the wrong replacement part.

Process: Performance Qualification

The purpose of equipment performance qualification is to provide rigorous testing to demonstrate the effectiveness and reproducibility of the process. In entering the performance qualification portion of validation, the process specifications should be established and have been proven acceptable through laboratory trials and that the equipment has been deemed acceptable on the basis of proper installation qualification studies.

Each process should be defined and described with sufficient specificity so that employees understand what is required. Parts of the process that may vary so as to affect important product quality should be challenged. In challenging a process to assess its adequacy, it is important that challenge conditions simulate those that will be encountered

during actual production, including worst-case conditions. The challenges should be repeated enough times to ensure that the results are meaningful and consistent.

Each specific manufacturing process should be appropriately qualified and validated. There is an inherent danger in relying on what are perceived to be similarities between products, processes, and equipment without appropriate challenge.

Formal Review

After actual production material has passed product performance qualification, a formal review should be performed to evaluate the following:

- Comparison of the product specifications and the actual qualified product
- Determination of the validity of test methods used to determine compliance with the product specifications
- Determination of the adequacy of the specification change control program

There should be a quality assurance system in place that requires revalidation whenever there are changes in formulation, equipment, or processes that could affect the product or its characteristics. Also for changes in raw material supplier, the manufacturer should consider differences in the raw material properties.

One way of detecting the kind of changes that should initiate revalidation is the use of tests and analysis methods that are capable of measuring these variable characteristics. Such tests and methods usually yield specific results that go beyond the mere pass/fail basis, thereby detecting variations within product and process specifications and allowing determination of whether a process is slipping out of control.

The quality assurance procedures should establish the circumstances under which revalidation is required. These may be based upon equipment, process, and product performance observed during the initial process validation. It is desirable to designate individuals who have the responsibility to review product, process, equipment, and personnel changes to determine if and when revalidation is needed.

The extent of revalidation depends upon the nature of the changes and how they affect the different aspects of production that were previously validated. It may not be necessary to revalidate an entire process. It may only be necessary to revalidate specific subprocesses that have been altered. Take the time to assess the nature and extent of the change and to determine the potential effects as part of the revalidation effort.

Documentation

It is essential that the validation program is documented and that the documentation is properly maintained. Approval and release of the process for use in routine manufacturing should be based upon a review of all the validation documentation, including data from the equipment qualification, process performance qualification, and product/package testing, to ensure compatibility with the process.

■ Suggested Reading

Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, 8th ed., by Loyd V. Allen, Howard C. Ansel, and Nicholas G. Popovich.

Encyclopedia of Pharmaceutical Technology, Vol. 18, by James Swarbrick (Ed.).

Fundamentals of Early Clinical Drug Development: From Synthesis Design to Formulation, by Ahmed F. Abdel-Magid and Stephane Caron.

Handbook of Pharmaceutical Excipients, by Raymond C. Rowe, Paul J. Weller, and Paul J. Sheskey.

Handbook of Pharmaceutical Manufacturing Formulations, by Sarfaraz K. Niazi.

Handbook of Pharmaceutical Manufacturing Formulations: Compressed Solid Products (Vols. 1–6) by Sarfaraz K. Niazi (Ed.).

Handbook of Preformulation: Chemical, Biological, and Botanical Drugs, by Sarfaraz K. Niazi.

Pharmaceutical Dosage Forms: Tablets, 2nd ed., Vol. 2, by Herbert A. Lieberman and Schwartz L. Lachman.

Pharmaceutical Salts: Properties, Selection, and Use, by P. Heinrich Stahl (Ed.), Heinrich Stahl, and Camille G. Wermuth (Ed.).

Pharmaceutical Unit Operations: Coating, by Kenneth E. Avis (Ed.), Steven Strauss, Rong-Kun Chang, and Atul J. Shukla (Ed.).

Remington: The Science and Practice of Pharmacy, by David B. Troy (Ed.) and University of the Sciences in Philadelphia (USP) Staff.

