such as those passing #100 mesh, is required to fill in the gaps in a good compaction process; however, a large proportion of fines (as they are called) can create a problem in the flow or compaction of material. As a result, many master formulas require the reworking of fines back to granules. Any such recommendation should be carried out considering the type of processing and equipment used. These are mere suggestions; if a product compacts well, then it has the right proportion of fines.

XXIV. FORMULA EXCESSES

The difference between the scale and the quantity used for manufacturing is a result of either adjustment for the chemical form used (such as salt form for labeled base), hydrate forms (to compensate for additional water), potency variations (such as for antibiotics and biologicals), manufacturing excesses (for losses of drug during manufacturing), stability excesses (to compensate for loss during the shelf life; this is most important for vitamin products), and solvent/hydration loss (such as during manufacturing).

XXV. GEOMETRIC DILUTION

In all instances where low-dose drugs are manufactured, the mixing of ingredients should be done in a geometric dilution process; for example, a tablet containing 100 mg per tablet will first require mixing the active drug with a smaller quantity of excipient and then building up the volume to make sure the API is properly distributed. Further consistency to the product is imparted during the mixing of the granulated mixture.

XXVI. GRANULATION/MIX ANALYSIS

A critical step in the manufacture of an oral solid dosage form is the blending of the final granulation. If uniformity is not achieved at this stage, then one could assume that some dosage units would not comply with uniformity requirements. The major advantage of blend analysis (from a uniformity perspective) is that specific areas of the blender that have the greatest potential to be nonuniform can be sampled. This is particularly true of the ribbon-type blender and planetary or pony-type mixers.

In some cases, such as for large or tumbler-type blenders, it is impractical to sample from the blender directly. In such cases, granulations or blends could be sampled at the time of blender discharge or directly from drums. If sampling from drums, samples from the top, middle, and bottom of each drum should be collected.

In most cases, sampling thieves are readily available for sampling the small quantities that need to be taken from key areas of the blender or the drums. If samples larger than one dosage unit must be collected, however, adequate provisions must be made to prevent excessive handling manipulation between the time of sampling and the time of analysis.

Good science and logic would seem to dictate that sample sizes of the approximate equivalent weight of the dosage unit should be sampled in order to test for uniformity. Many industrial pharmacy and engineering texts confirm this approach. Large granulation sample sizes, such as 1 oz, will provide little information with respect to uniformity. Generally, further mixing after sampling and prior to analysis can yield misleading results.

The acceptance criteria for granulation dose uniformity testing needs to be continuously evaluated. Although many manufacturers evaluate dose uniformity using the compendia dose uniformity specifications (85–115% with an RSD of 6–7.8), such specifications should be tighter where supported by the firm's historical data on the level of blend uniformity with its equipment for a given product. In many cases, compendia assay limits for the finished product (90–110% of label claim) are broad enough for this purpose, and most manufacturers should be able to demonstrate blend assay results well within these limits. If larger sample sizes are taken for assay to evaluate total composite assay, then the specific USP or filed criteria for assay should be used.

In addition to the analysis of blends for dose uniformity and potency, blends are tested for physical characteristics.

A major physical parameter used to demonstrate equivalence between batches is the particle size profile. This is particularly important for comparison of the biobatch with production batches and should be repeated when processes are modified or changed. The particle size profile will provide useful information for demonstrating comparability.

Particle size profiles are particularly important for the tablet made by a wet granulation process. The size and even the type of granule can affect the pore size in a tablet as well as its dissolution. For example, dissolution failure may be attributed to a change in the milling screen size, yielding a granulation with larger granules. When coated, larger pores permit increased penetration into the tablet by the coating solution, resulting in slower dissolution.

Another test typically performed on the granulation, particularly when the wet granulation process is used, is loss on drying (LOD) and moisture content. If organic solvents are employed, then residual solvent residues are also tested. In the validation of a drying process, LOD levels are determined before, during, and after drying in order to demonstrate times and levels. As with processing variables, levels (specifications) are established in the development phase, with the validation phase used to confirm the adequacy of the process.

XXVII. INGREDIENT WARNING

Whereas many organic solvents are removed, traces may remain, and these may cause reactions, particularly in children; additionally, appropriate consideration should be given to the choice of using lactose for its intolerance in some of the use of sulfites or preservatives to which patients may be allergic.

XXVIII. IN-PROCESS TESTING

In-process testing is the testing performed on dosage forms during their compression/encapsulation stages to assure consistency throughout these operations. For tablets, individual tablet weights, moisture, hardness (compression force), and disintegration are performed. Because hardness and disintegration specifications are established during development and biobatch production, testing is performed to demonstrate equivalency (comparability) and consistency.

Specifications required to control the manufacturing process must be established and justified. This will require