

sampling techniques. This proposal recommends the use of stratified sampling of blend and dosage units to demonstrate adequacy of mixing for powder blends [24]. Stratified sampling involves the deliberate selection of units from various locations within a lot or batch or from various phases or periods of a process to obtain a sample. Such sampling specifically targets locations either in the blender or throughout the compression/filling operation where there is a high risk of failing content uniformity specifications.

Generally, differences observed between blend uniformity and drug-product content uniformity are less pronounced in wet granulation and compaction-type formulations compared to direct-compression formulations.

## FORMULATION DEVELOPMENT STRATEGIES

### PATENT SEARCH(ES)

In the early days of the generic industry, once the basic patent had expired, generic pharmaceutical companies were free to launch their version(s) of the drug product(s) into the market. However, over the last 20 or so years, the innovator drug companies have sought to extend their product(s) life, focusing initially on “Process Patents” (the route of synthesis, whereby the API is produced, including any unique crystal forms that may have resulted). The synthetic pathway has been explored to the fullest and the widest possible claims have been registered. The leading generic bulk API manufacturers continue their quest to synthesize APIs that do not infringe process patents. Although generic bulk drug manufacturers were, at one time, content merely to produce non-patent-infringing active(s), many have now taken it upon themselves to file patents of their own, a ploy that considerably increases the difficulty that other raw material manufacturers will face when attempting to synthesize the same active raw material.

### Formulation Patents

In certain instances, innovator drug companies have valid reasons for filing formulation patents, particularly where a specific excipient (or blend of excipients) lends a particular uniqueness in terms of release or stability [25]. However, some drug companies file patents that claim every excipient known, and such patents are clearly open to challenge.

It is more difficult to file formulation patents in the arena of immediate-release dosage forms than in the case of modified/controlled-release formulations, where creative solutions have been applied to modify the *in vitro* and *in vivo* release characteristics of active(s) to provide a dosage regimen that offers significant therapeutic advantages and improved patient compliance.

### Combination Patents

Combination patents are those that pertain to more than one active ingredient combined together in a single drug product, the resultant product ideally displaying a synergistic pharmacologic response compared with each active ingredient administered on their own. One of the earliest examples of such a combination was