written, the Master Manufacturing Document approved and signed off, the Process and Cleaning Qualification protocols written, and the third month's satisfactory informal stability results (which indicate drug product stability) generated, the exhibit-batch manufacture can be progressed.

Exhibit-Batch Production

Manufacture of the exhibit batch is the responsibility of the formulation scientist/technician(s) associated with the development of the final formulation together with the scale-up or "technical transfer" team. The formulation and process should be tested by manufacturing a subbatch using similar equipment as the scale-up equipment and using the same raw materials intended for exhibit-batch manufacture. For example, using a 15 kg capacity granulator, consider the need to manufacture 150,000 × 500 mg tablets (i.e., 75 kg batch size). In this case, five granulation sublots would be required (75/15 = 5) to complete the batch manufacture. Hence, one sublot or more can be used to optimize the granulation parameters, and once this has been done, these parameters are applied to the actual exhibit batch. In so doing, the granulation, drying, milling, and blending operations can be optimized in advance, thereby obviating the possibility of problems occurring during subsequent batch production.

This preliminary sub-batch must be progressed to completion and samples must be submitted to the laboratory to confirm both physical and chemical attributes of the dosage form. Only once the testing has revealed an acceptable comparison with the development batches produced to the same formula and process should the actual exhibit-batch manufacture be undertaken.

Clearly, all exhibit-batch manufacture is required to be carried out under current good manufacturing practice (cGMP) conditions [85].

Samples from the exhibit batch must be submitted to the laboratory, and only when the predetermined acceptance criteria have been met (imposed at both "Batch Release" and "Process Qualification" levels) can the generic product be randomized and subsequently packaged.

Randomization is required so that any bias in the manufacturing process is removed. This involves blending a batch of drug product in a blender of sufficient size, for example, a "drum roller" blender, following validation of the process. Validation involves the addition and mixing of an equal mass of tablets/capsules of the same size but different colors (red and blue, for example) and their distribution is evaluated after rotating the blender for a set number of revolutions. The process may be deemed to be validated if, after three consecutive tests, the different color drug products are uniformly distributed with approximately ±20% variation in the samples drawn (usually 100 units). For example, draw ten 100 tablet samples of the blended lot of red and blue tablets to characterize the blending process. Determine the number of red and blue units in each sample. Acceptable randomization would thus be 30:70 (red/blue) or 70:30 (red/blue). In the case of coated tablets, the rotation of the coating pan automatically confers acceptable randomization on the coated tablets.