Master Manufacturing Document

This document must be drawn up by a team comprising the formulation scientist and his/her counterpart in the exhibit-batch manufacturing section. Once agreement has been reached, a draft of the "Master" document is forwarded to Plant Operations for comment and acceptance.

A copy of the signed Master Manufacturing Document is then provided to the Process Validation Department for generation of the Process and Cleaning Qualification protocols. In general, the validation process requires at least three batches of each strength of drug product to be assessed, whereas the qualification process relates to a single batch of each strength of drug product only.

The Process Qualification Protocols must monitor and control all key processes in the manufacturing pathway such as the following:

- Volume and rate of addition of granulating vehicle
- Exact drying conditions
- Milling rates, screen sizes, etc.
- Blender rotation speeds and mixing times
- Blend uniformity after blending
- Blend uniformity after discharge of the granule into "holding bins" (to evaluate if active segregation has resulted on discharge)
- Granulometry assessments, bulk and tapped density determinations, and loss on drying measurements before and after granule discharge from the blender

Before compressing the batch of granules into tablets at the optimum hardness and speed, the following parameters need to be established:

a. "Low" and "high" hardness levels at which the tablets can be compressed meeting all predetermined acceptance criteria, with specific reference to dissolution profiles.
b. The highest speed at which the particular press can be operated to provide tablets meeting predetermined acceptance criteria, with specific reference to content uniformity.
c. Humidity and temperature (these are controlled in plant operations by standard operating procedures, whereas specific conditions are imposed by product-specific demands during formulation development).

Samples must be drawn at predetermined intervals during the compression cycle and then grouped into sets reflecting the beginning, middle, and end of the run. Samples from each stage must be tested for assay, content uniformity, and dissolution profile in addition to full physical characterization (hardness, disintegration, friability, average weight, individual weights, etc.).

A Qualification Report embracing all the results must be completed once the batch(es) has been manufactured and the analyses have been completed.

Once the specifications have been set, the API and excipients ordered, received, and tested, the necessary tooling received and verified, the Development Report