TABLE 23.8 (*Continued*)
List of Quality Attributes and Potential Process Parameters for a Wet Granulation Process

Process Step	Product Quality Attributes	Measure (Units)	Process Parameter (Variables)	Rationale
9. Film coating	Appearance Assay Water content Mechanical integrity Microbial limit test	Defect rate—Visual (AQL testing) Analytical test (mg/g or % LC) KF (%) Defect rate FU/g	Weight gain Inlet and outlet temperatures Spraying rate Inlet air humidity Atomizing air pressure Pan speed	Impacts final drug product quality and regulatory requirements
10. Finished tablets	Content uniformity Assay Purity Disintegration Dissolution Appearance Friability	Analytical technique (% rsd) Analytical technique (mg/g) Analytical technique (% impurity) Time USP %Q in minutes		Requirement for final drug product disposition decision

and process variables or parameters. Once the entire process diagram is laid out, a systematic approach is utilized to gauge the impact of variables on the product attributes. This is performed by ranking the desired attributes on a scale of 1–10, with 10 being very important to the customer and regulatory agency and 1 important from a process-understanding perspective. Through this exercise, the key product attributes are identified as focal points to measure the impact of various process parameters.

Cause-and-effect diagrams (Food and Drug Administration, 1987; Chao et al., 1993) provide another way of pictorially representing the main processing steps with process parameters that may have an effect on the key product attribute. For example, in a wet granulation step, the load size, impeller rpm and duration, and granulation liquid volume/addition rate may have an effect on the overall content uniformity and dissolution profiles, which is critical for water-insoluble candidates of the dosage form. A cause-and-effect diagram of the entire process provides a guideline and overall understanding of the various key parameters that may impact a common quality attribute such as content uniformity. It is important, however, to understand that not all parameters will have a significant impact on the desired quality attribute. The next step in the process optimization is to determine which parameter influences the quality attributes most, and what would be the acceptable range to control the parameter so as to meet the quality attribute consistently time after time. This systematic analysis is performed to develop an influence matrix and to define the strength of the relationship between variables and response as strong (S), moderate (M), weak (W), or none (N). Construction of such a matrix identifies those variables that have the greatest influence on the desired quality attribute. Design of experiments and statistical analyses of the data are tools available to scientists to determine key process parameters and develop sound understanding of the manufacturing process.

These studies are essential parts of regulatory dossiers, independent of batch or continuous manufacturing.