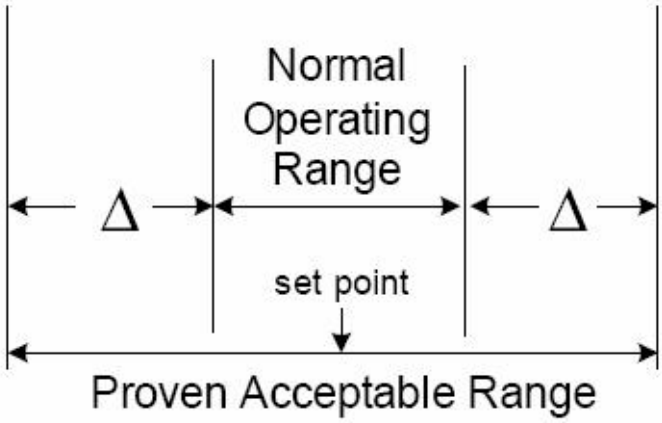
Figure 1

Figure 1 is a useful reference to understand the critical process parameter ranges.



2. Validation Protocol Contents should include or reference, at least, the following:

- Validation approach to be used (e.g., prospective, concurrent, matrixing, bracketing, retrospective) with justification for approach chosen;
- Brief description of product, including product name, dosage form, and strength where applicable;
- Master manufacturing instructions or Device Master Record (DMR) to be validated;
- Brief description of process with a summary and/or process flow diagram of critical processing steps to be evaluated and critical parameters to be monitored;

  Acceptance criteria for the following:

  - Acceptability (meeting established critical quality attributes and specifications);

  - The number of consecutive successful validation batches/lots needed to show consistent control of the process.

  - Equivalency to existing drug products (where applicable) by comparison to previously produced batches/lots (commercial, development, or biobatches).

  - Requirements to conduct homogeneity and hold time studies, if applicable;

- Sampling plan, including type, amount, and number of samples, together with any special sampling or handling requirements.

- Critical process parameters and operating ranges, including justification for these

10. Major Changes -examples of major changes to an established process that require consideration of revalidation include, and are not limited to, the following:

- Process changes that can affect the release, metering, or other characteristics of the dose delivered to the patient, for example:
  - Changes to Active Pharmaceutical Ingredients (API) and critical excipients (change in API Site or manufacturer, route of synthesis for APIs, impurity profile, chemical or physical characteristics); and
  - Major facility changes (e.g., Site, new aseptic area);
- Changes to major equipment such as size, design, or principle of operation;
- Changes in the acceptable range of a critical process parameter or a planned shift of the NOR that increases the risk of deviation and has the potential to adversely impact product quality;
- New reworking and/or reprocessing procedure;
- Fundamental change to manufacturing process or technology, for example:
  - Batch/lot size;
  - Dry to wet granulation or vice versa;
  - Change from one type of drying process to another (e.g., oven tray, fluid bed, microwave);
- Changes that could affect acceptable microbiological quality of the drug product;
- For medical devices, any change that affects form, fit, or function of the device (e.g., material, components, manufacturing or assembly processes, and replacement of equipment); and
- Biopharmaceutical -example(s) such as filtration, concentration or mixing parameters, lengthening maximum hold time, and shipping conditions.

Changes in the process that result in a change in the Regulatory Process Description (RPD) should be addressed through the change management system.

11. Minor Changes may require consideration of revalidation or completion of supplemental studies to support the change. Examples of minor changes include, and are not limited to, the following:

- Changes to equipment with the same design and operating principle;
- Changes, which are unlikely to have measurable impact on product quality or performance, as determined by risk assessment;
- Change within a single Site using the same equipment as previously validated;
- Change in existing code imprint (e.g., changing from numeric to alphanumeric, addition of an ink code imprint, or change to ink used for a solid dosage form where the ink is already used on approved products); and
- Change of imprint by embossing, debossing, or engraving on a solid dosage drug product, with the exception of modified release dosage forms.

If validation is being carried out as a result of a change to an existing process, documented justification should be provided in the validation protocol if any of the above applicable parameters are not to be assessed.

16. Oral Solutions and Suspensions include drug products such as elixirs, emulsions, solutions, gels, syrups, tinctures, and suspensions.

The process validation protocol for oral solutions and suspensions should include assessment of, at least, the following:

- In-process assay of bulk before filling (where applicable);
- Homogeneity sampling plans should include representative samples from:
  - Throughout the bulk suspension;
  - Top and bottom of solutions, and
  - During the filling operation;
- Rheological properties such as viscosity, thixotropy (where applicable);
- Potency;
- Fill volume, including assessment of consistency and reproducibility of filling process; and
- Other tests such as pH, specific gravity, and refractive index, as applicable.

If validation is being carried out as a result of a change to an existing process, documented justification should be provided in the validation protocol if any of the above applicable parameters are not to be assessed.

17. Semi-Solid Drug Products include suppositories and topical drug products such as emulsions, gels, lotions, creams, ointments, and transdermal patches.

The process validation protocol for semi-solids should include assessment of, at least, the following:

- Solubility of API in carrier vehicle, where applicable;
- Microbiological purity, including an assessment of consistency between batches/lots of microbial levels and isolated organisms;
- Fill volume, generally an in-process measurement based on bulk density;
- Rheological properties such as viscosity, thixotropy, (where applicable);
- Appearance (for example, absence of grittiness, smooth, phase separation);
- Potency; and
- For transdermal products (patches) adhesion, package integrity, and dose uniformity should also be considered.

If validation is being carried out as a result of a change to an existing process, documented justification should be provided in the validation protocol if any of the above applicable parameters are not to be assessed.

18. Oral Solid Dosage Forms - validation should include an evaluation of any critical mixing, granulation, milling, drying, blending, compression or encapsulation, coating,

