R. Significant body of information

A significant body of information on the stability of the drug product is likely to exist after 5 years of commercial experience for new molecular entities, or 3 years of commercial experience for new dosage forms.

S. Validation

Establishing through documented evidence a high degree of assurance that a specific process will consistently produce a product that meets its predetermined specifications and quality attributes. A validated manufacturing process is one that has been proven to do what it purports or is represented to do. The proof of validation is obtained through collection and evaluation of data, preferably beginning from the process development phase and continuing through into the production phase. Validation necessarily includes process qualification (the qualification of materials, equipment, systems, buildings, and personnel), but it also includes the control of the entire processes for repeated batches or runs.

III. Components and Composition

This section of the guidance focuses on changes in excipients in the drug product. Changes in the amount of drug substance are not addressed by this guidance. Changes in components or composition that have the effect of adding a new excipient or deleting an excipient are defined at Level 3 (defined below), except as described below.

A. Level 1 Changes

1. Definition of Level

Level 1 changes are those that are unlikely to have any detectable impact on formulation quality and performance.

Examples:

a. Deletion or partial deletion of an ingredient intended to affect the color or flavor of the drug product; or change in the ingredient of the printing ink to another approved ingredient.

b. Changes in excipients, expressed as percentage (w/w) of total formulation. less than or equal to the following percent ranges:

EXCIPIENT	PERCENT EX- CIPIENT (w/w) OUT OF TOTAL TAR- GET DOSAGE FORM WEIGHT
Filler	±5
Disintegrant	
Starch	±3
Other	±1
Binder	±0.5
Lubricant	
Calcium (Ca) or Magnesium	±0.25
(Mg) Stearate	
Other	±1
Glidant	
Talc	±1
Other	±0.1
Film Coat	±1

These percentages are based on the assumption that the drug substance in the

drug product is formulated to 100% of label/ potency. The total additive effect of all excipient changes should not be more than 5 percent. (Example: In a product consisting of active ingredient A, lactose, microcrystalline cellulose, and magnesium stearate, the lactose and microcrystalline cellulose should not vary by more than an absolute total of 5 percent (e.g., lactose increases 2.5 percent and microcrystalline cellulose decreases by 2.5 percent) relative to the target dosage form weight if it is to stay within the Level 1 range).

The components (active and excipients) in the formulation should have numerical targets that represent the nominal composition of the drug product on which any future changes in the composition of the product are to be based. Allowable changes in the composition should be based on the approved target composition and not on previous Level 1 changes in the composition.

2. Test Documentation

a. Chemistry Documentation Application/compendial release

- requirements and stability testing. Stability testing: One batch on long-term
- stability data reported in annual report. b. Dissolution Documentation
- None beyond application/compendial requirements.
- c. In Vivo Bioequivalence Documentation None.
- 3. Filing Documentation

Annual report (all information including long-term stability data).

B. Level 2 Changes

1. Definition of Level

Level 2 changes are those that could have a significant impact on formulation quality and performance. Tests and filing documentation for a Level 2 change vary depending on three factors: Therapeutic range, solubility, and permeability. Therapeutic range is defined as either narrow or non-narrow. A list of narrow therapeutic range drugs is provided in Appendix A. Drug solubility and drug permeability are defined as either low or high. Solubility is calculated based on the minimum concentration of drug (milligram (mg)/mL), in the largest dosage strength, determined in the physiological pH range (pH 1 to 8) and temperature (37±0.5°C). High solubility drugs are those with a dose/ solubility volume of less than or equal to 250 mL. (Example: Compound A has as its lowest solubility at 37±0.5 °C, 1.0 mg/mL at pH 7, and is available in 100 mg, 200 mg, and 400 mg strengths. This drug would be considered a low solubility drug as its dose/solubility volume is greater than 250 mL (400 mg/1.0 mg/mL=400 mL). Permeability (Pe, centimeter per second) is defined as the effective human jejunal wall permeability of a drug and includes an apparent resistance to mass transport to the intestinal membrane. High permeability drugs are generally those with an extent of absorption greater than 90 percent in the absence of documented instability in the gastrointestinal tract, or those whose permeability attributes have been determined experimentally.

Examples:

a. Change in the technical grade of an excipient. (Example: Avicel PH102 versus Avicel PH200.)

b. Changes in excipients, expressed as percent (w/w) of total formulation, greater than those listed above for a Level 1 change but less than or equal to the following percent ranges (which represent a twofold increase over Level 1 changes):

EXCIPIENT	PERCENT EX- CIPIENT (w/w) OUT OF TOTAL TAR- GET DOSAGE FORM WEIGHT
Filler	±10
Disintegrant	
Starch	±6
Other	±2
Binder	±1
Lubricant	
Ca or Mg Stearate	±0.5
Other	±2
Glidant	
Talc	±2
Other	±0.2
Film Coat	±2

These percentages are based on the assumption that the drug substance in the drug product is formulated to 100 percent of label/potency. The total additive effect of all excipient changes should not change by more than 10 percent.

The components (active and excipients) in the formulation should have numerical targets that represent the nominal composition of the drug product on which any future changes in the composition of the product are to be based. Allowable changes in the composition should be based on the approved target composition and not on the composition based on previous Level 1 or Level 2 changes.

2. Test Documentation

a. Chemistry Documentation

Application/compendial release

requirements and batch records. Stability testing: One batch with 3 months

accelerated stability data in supplement and 1 batch on long-term stability.

b. Dissolution Documentation

Case A: High Permeability, High Solubility Drugs

Dissolution of 85 percent in 15 minutes in 900 mL of 0.1*N* HCl. If a drug product fails to meet this description, the applicant should perform the tests described for Case B or Case C (below).

Case B: Low Permeability, High Solubility Drugs

Multi-point dissolution profile should be performed in the application/compendial medium at 15, 30, 45, 60, and 120 minutes or until an asymptote is reached. The dissolution profile of the proposed and currently used drug product formulations should be similar.

Case C: High Permeability, Low Solubility Drugs