

- (1) Shipment of the dosage form to the packaging site and the receipt protocol (Certificate of Analysis and/or testing) by the packaging site.
 - (2) Storage conditions and time at the packaging site.
 - (3) Packaging operations and in-process controls.
 - (4) Release testing of and/or controls on the finished drug product by the packaging site.
2. Regarding the in-process controls and tests:
- a. In-process control points should be identified in each segment of the "Manufacturing Process Flow (Proposed Commercial Production)" (Volume 1.2, page 03-041). For each in-process control point, the test, test method, and specification must be provided.
 - b. In-process control points should be identified in the packaging of the dosage form that results in the finished drug product.
3. Regarding reprocessing operations, a statement concerning drug product and drug product intermediate reprocessing must be provided. If reprocessing is conducted, the details as to the decision process and reprocessing protocol(s) must be submitted along with the scientific data supporting the reprocessing.
4. Regarding the container/closure system, the following must be provided:
- a. A letter of authorization (LOA) for the following DMFs:
 - i. [REDACTED]
 - ii. [REDACTED]
 - b. The exact details for the test method used to evaluate the formed finished commercial unit-dose package (blister and pouch style) with respect to moisture permeation.
 - c. The exact details for the test method used to evaluate the consistency of seal integrity and the test method used to measure the moisture permeability of the package seal for the finished commercial unit-dose package.
 - d. The make, model number, and principle of operation for the test equipment for each

test employed for the evaluation of finished commercial blister and pouch unit-dose packages.

5. Regarding the package interchangeability protocol:

a. The introductory paragraph to this protocol must include conditions to the effect that full shelf life studies must be completed and evaluated before the interchangeability protocol for the drug product is used. Each subsequent package change to the approved package must be evaluated through full shelf life data before any additional changes to the packaging are instituted. In addition, commit to including the package interchangeability protocol with prior approval supplements for changes in the drug product formulation and/or chemistry, manufacturing, and controls for the drug substance and/or drug product.

b. Concerning the section titled "A. Proposed Changes" (Volume 1.2, page 03-143):

i. For the HDPE Bottles:

(1) The range of HDPE bottle sizes and mouth openings must be stated. Be advised that additional drug product release testing may be necessary for containers of [REDACTED].

(2) The new resin must be an [REDACTED]. In addition, there must be an LOA to a DMF for the new resin and/or supplier and the DMF must have an acceptable status as determined by the Agency for supplying the [REDACTED] for drug product packaging.

ii. For the [REDACTED]:

(1) The range of [REDACTED] potential cap sizes must be stated along with the closure type.

(2) The new resin must be a [REDACTED]. In addition, there must be an LOA to a DMF for the new resin and/or supplier and the DMF must have an acceptable status as determined by the Agency for supplying polypropylene resin for drug product packaging.

iii. For the [REDACTED]:

(1) The range of the [REDACTED] size must be stated.

(2) The [REDACTED] surface in contact with the drug product must be of the

same class of material as the original [REDACTED]. In addition, there must be an LOA to a DMF for the new [REDACTED] and/or supplier and the DMF must have an acceptable status as determined by the Agency for supplying the inner seal/liner.

- iv. For the unit dose packages:
- (1) There must be stated limits and a scientific justification for the limits for any change to the thickness and dimensions of the unit dose package.
 - (2) There must be an LOA to a DMF for a new [REDACTED] of the same general type as in the original application and the DMF must have an acceptable status as determined by the Agency for supplying the new [REDACTED].
 - (3) A new supplier of blister/backing/pouch must provide an LOA to a DMF and the DMF must have an acceptable status as determined by the Agency for supplying the blister/backing/pouch.
- c. Concerning the section titled "B. Stability Studies" (Volume 1.2, page 03-144), there must be a protocol commitment to full shelf life stability studies using the "Post Approval Stability Program for Commercial Product" (Section 3.5.7, Volume 1.2, page 03-163). In addition, the commitment must state that you will withdraw from the market place any drug product that fails stability testing and that all the stability data will be submitted in the annual report.
- d. Concerning the section titled "C. USP Testing" (Volume 1.2, page 03-144), the package interchangeability protocol must include the specific test, test methods, and specifications to be initiated and reported:
- i. Upon receipt of raw materials used to manufacture the finished drug product package.
 - ii. To verify that the new finished drug product package is equivalent or better than the previous market package.
- e. Concerning the section titled "D. Information to be submitted to the FDA," the annual report information, in addition to including Sections 5.c. and 5.d. above, should include a comparison of the data collected for the new container system versus the old container system for both the raw materials used to manufacture the finished drug product and the finished drug product package.
- f. Concerning the section titled "E. Statistical Process Control (SPC)," a detailed