Attachment 2: Data Set Requirements for Common Changes

Comparability Protocol
Sample Data Requirements - #1

New rubber stopper compound as an alternate to the current approved stopper. Such a change would be applicable across an entire product line. The data package should include:

- Specifications and Certificate of Analysis for the new stopper; include copies of the applicable test methods;
- One commercial-scale batch of drug product at the approved facility, filled and finished with the current approved commodities; one commercial-scale batch for each list number (or fill size);
- Certificate of Analysis for each commercial-scale batch;
- Stability protocol/testing matrix; include upright and inverted vials, 40°C & 25°C at standard intervals;
- Scientific report containing a minimum of three months of accelerated stability data;
- Material evaluation of the stopper, including USP Biological Reactivity, USP Systemic and Intracutaneous Toxicity, Cytotoxicity and USP Physiochemical tests;
- Sterility assurance package including depyrogenation study of the proposed stopper;
- Blank batch record for each drug product list number (or fill size);
- Executed batch record for each drug product list number (or fill size); and
- Specifications and methods referenced in the above studies.

Comparability Protocol
Sample Data Requirements - #2

New API (drug substance) vendor as an alternate or replacement to the current approved vendor. Such a change would be applicable across an entire product line. The data package for an alternate vendor of a bulk drug should include:

- Copy of the FDA's Establishment Inspection report for new vendor; this information may or may not be available from the new vendor. Typically contained in the vendor's Type II DMF or is considered proprietary in nature;

- Overview of the manufacture of the drug substance (current versus new vendor process) with differences explained;

- Impurity profile comparison at either the drug substance or drug product stage; data should be a side by side comparison of all attributes to demonstrate comparability and equivalence of the drug substance manufactured at the two facilities; comparison should be of historical API (minimum of three consecutive lots) versus new API (minimum of three consecutive lots); comparable quality consists of comparable particle size distribution, polymorphic form, impurity profile and other physiochemical properties;

- Updated components and composition statement, if applicable, if creating a new drug code for new vendor API;

- Updated raw materials and controls section: provide new vendor's name and address, Type II DMF Letter of Authorization, supplier's COA, specifications and data for API manufactured by the new vendor, including spectra and chromatograms;

- Updated facilities address section: provide new vendor's address, including brief description of the facility, GMP certification letters, debarment certification letter (if applicable) and Central File Number;

- Blank master batch records for the largest intended commercial batch size for all impacted list #s- one example for each configuration versus each list #;

- Executed batch records: one executed batch record for all impacted list numbers;

- Certificates of Analysis for finished drug product;

- Analytical methods for the API;

- Stability protocol/testing matrix: include upright and inverted; 40°C and 25°C at standard intervals;

Comparability Protocol
Sample Data Requirements - #2
(Continued)

- Stability data/report: if change is limited to an alternate manufacturing site where impurity profile comparison demonstrates equivalent drug substance or drug product, and similar equipment and manufacturing processes are used, stability data on the drug substance may not be necessary; provide the standard stability commitment to conduct long term stability studies in accordance with the approved marketed product stability protocol on the first commercial production batch of drug product made with the new drug substance; include results from some accelerated stability data; and

- Statistical analysis comparison: build this in as a requirement for New Drug Division submissions - analysis of impurities, etc of historical API (minimum of three consecutive lots) versus new API (minimum of three consecutive lots).

Comparability Protocol
Sample Data Requirements - #3

Alternate manufacturing site (alternate company site, USA or Puerto Rico, or from contract manufacturer to company site) for the Drug Product. The sample data requirements reflect a drug product manufactured at more than one product strength. The data package should include:

- Copy of the FDA's Establishment Inspection report for new manufacturing site and/or cGMP and debarment certification letters;

- The manufacturing and controls section, including components and compositions, process, container/closure system, test methods and specifications, are the same as in the current approved NDA. Additionally, the equipment used in the manufacture of the drug product is of the same design and operating principle. Only the manufacturing site for the finished product is new;

- Microbiology/sterility assurance package;

- Blank master batch records;

- Executed batch records: three (pilot) batch records for the lowest product strength and three (pilot) batch records for the highest product strength;

- Certificates of Analysis for each lot of finished drug product;

- Stability data of the finished dosage form: a bracketing approach can be utilized for the stability studies. Three (pilot) batches of the lowest product strength and three (pilot) batches of the highest product strength should be manufactured and placed on stability (25°C/60%RH) at standard intervals; provide a comparison of stability data of the drug product from the current approved facility and the new manufacturing site; provide three months of stability data;

- Commercial stability study commitment: three commercial batches for each product strength utilizing the approved marketed product stability protocol;

- Expiration date; and

- Labeling: revise to correctly reflect "Manufactured for XXX, City, State, ZIP Code, USA" or "Manufactured by XXX, City, State, ZIP Code, USA."