Once the bioequivalence review is completed and all bioequivalence requirements are addressed, the DBE archives an acceptable letter that states that there are no further questions at this time. Additionally, the APM is notified electronically that the bioequivalence review is complete. If the bioequivalence review indicates deficiencies, a deficiency letter is issued to the applicant.

Bioequivalence studies with clinical endpoints are often recommended to establish bioequivalence between dosage forms intended to deliver the active ingredient(s) locally (i.e., topical creams and ointments) and between dosage forms that are not intended to be absorbed (i.e., rifaximin tablets, 200 mg) (21 CFR 320.24(b)(4)). The OGD's Director, Division of Clinical Review (DDCR) and the clinical team review these studies for the DB. The DDCR also forwards all comments and recommendations to the Director of the DB for concurrence. The DDCR consults with the Office of New Drugs for input on the appropriateness of clinical endpoints (see MaPP 5210.4). For this reason, it is strongly advised that applicants submit protocols or bio-INDs before the initiation of bioequivalence studies with clinical endpoints to ensure the appropriateness of study designs and endpoints (see MaPP 5240.4).

CHEMISTRY REVIEW PROCESS

After an ANDA has been accepted for filing by the RSB, the Chemistry, Manufacturing and Controls (CMC) section of the application is assigned to the appropriate Chemistry Division and Team based on the therapeutic category of the drug product. Once the application is assigned to the team, the application is designated as "random" and placed on the team leader's queue. The APM assigns the application to a reviewer on his or her team according to the "first-in, first reviewed policy." The Chemistry Divisions review the CMC section of ANDAs, Drug Master Files, Supplemental ANDAs, Annual Reports, and Controlled Correspondence.

The Chemistry Divisions are organized into review teams consisting of five or six primary reviewers, a team leader, and the APM. Team leaders perform a secondary review of all chemistry submissions. An APM assigned to each team coordinates the entire review process and acts as the primary point of contact for the application. Each division is led by a Division Director and Deputy Director. A tertiary review is often performed by the Deputy Director, but may be performed by the Division Director, to ensure consistent recommendations to applicants. Interdivisional consistency is also emphasized through regular meetings between the Chemistry Divisions and the OGD management.

The goal of the chemistry review process is to assure that the generic drug will be manufactured in a reproducible manner under controlled conditions. Areas such as the applicant's manufacturing procedures, raw material specifications and controls, sterilization process, container and closure systems, and stability data are reviewed to assure that the drug will perform in an acceptable manner.

The chemistry reviewer drafts a primary review that is forwarded to the team leader for secondary review. The secondary review may require little or no revision from the first draft or it may require major revision. Team leaders provide comments and corrections to the primary reviewer. The APM also assists in the correction