CENTER FOR DRUG EVALUATION AND RESEARCH

Guidance for Industry

The FDA published Good Guidance Practices in February 1997. This guidance was developed and issued prior to that date.

Additional copies are available from:
Office of Training and Communications
Division of Communications Management
Drug Information Branch, HFD-210
5600 Fishers Lane
Rockville, MD 20857

(Tel) 301-827-4573
(Internet) http://www.fda.gov/cder/guidance/index.htm

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, FOOD AND DRUG ADMINISTRATION

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

JUL 1 1992

Dear Sir or Madam:

The purpose of this letter is to provide you with some important information from the Office of Generic Drugs (OGD) concerning: 1) new bioequivalence guidances; and 2) OGD's recent experience with refuse-to-file letters.

1. Bioequivalence Guidances

OGD has recently issued two new bioequivalence guidances that may be of interest to you. The first, "Statistical Procedures for Bioequivalence Studies Using a Standard Two-Treatment Crossover Design," provides information about new recommendations for statistical analyses of bioequivalence data for sponsors of ANDA's and AADA's. The guidance addresses three specific aspects of statistical analysis of bioequivalence studies discussed by the Generic Drugs Advisory Committee in September, 1991:

a. Logarithmic transformation of pharmacokinetic data;

b. Sequence effect; and

c. Outlier analysis.

This Guidance becomes effective July 1, 1992. Any investigations initiated after that date should generally conform to the recommendations of the Guidance.

The second guidance, "Interim Guidance Topical Corticosteroids *In Vivo* Bioequivalence and *In Vitro* Release Methods," provides recommendations to pharmaceutical sponsors on methods to document bioequivalence and quality control of topical corticosteroids. The Interim Guidance also takes effect July 1, 1992.

You may request copies of these Guidances by calling or writing to:

Executive Secretariat Staff
(MPN-1) HFD-8
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857
(301) 295-8012

2. Refuse to File Letters

On November 8, 1991, OGD notified you that we intended to tighten our pre-filing screening criteria for ANDA's and AADA's. The purpose of this change was to ensure that scarce OGD resources would not be wasted on applications that did not meet minimal acceptance standards and to provide early notification to sponsors of deficiencies that might otherwise not be identified for several months. My staff recently conducted an analysis of our experience with the new criteria and the results of that evaluation are provided in Enclosure 1. The results are based on analysis of 35 refuse-to-file letters issued between December, 1991 and May, 1992. OGD hopes that by providing you with the results, you can see the effects of the program and can direct your attention to preventing some frequently recurring deficiencies.

The Office of Generic Drugs appreciates your consideration of this information.

Sincerely,

Roger L. Williams, M.D.
Director, Office of Generic Drugs

REASONS FOR AND FREQUENCY OF REFUSE TO FILE LETTERS
(DECEMBER 1991- MAY 1992)

REASON	FREQUENCY
NO EXECUTED BATCH RECORDS	9
NO AUTHORIZATION OF A U.S. AGENT FOR THE DMF	9
NO CERTIFICATE OF ANALYSIS FOR INGREDIENTS	8
NO MASTER PRODUCTION BATCH RECORDS	7
NO INFORMATION TO SHOW EQUIVALENCY TO LISTED DRUG	5
NO CGMP CERTIFICATION	4
NO STABILITY DATA	4
EXCLUSIVITY RIGHTS NOT ADDRESSED	4
NO ENVIRONMENTAL IMPACT ANALYSIS	3
SPECIFICATION TEST NOT DESCRIBED	3
NO SAMPLE STATEMENT	3
NO METHODS VALIDATION	2
NO ENGLISH TRANSLATION	2
NO MANUFACTURING CONTROLS	2
NO PRODUCTION SITE IDENTIFICATION	2
NO COMPARATIVE DISSOLUTION DATA	2
NO STABILITY PROTOCOL	1
356H WAS A JOINT SUBMISSION	1
TAB DIFFERED IN COLOR THAN THOSE IDENTIFIED IN ANDA	1
EXCESSIVE DEFICIENCIES	1
PRODUCTION STRENGTH EXCEEDS RECOMMENDED LEVEL	1
NEED TO SUBMIT SEPARATE ANDAs FOR EACH STRENGTH	1
NO COMPONENTS OR COMPOSITION	1
NOT IN COMPLIANCE WITH PARAGRAPH FOUR CERTIFICATION	1
TOTAL 22 (REASONS)	**77**