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

June 1, 1990

To all NDA or ANDA Holders and Applicants

Dear Sir or Madam:

This letter is intended to continue the series of efforts to communicate interim and informal generic drug policy and guidance. This effort began with a letter from Harry M. Meyer, Jr., M.D., dated October 11, 1984, shortly after passage in 1984 of the Drug Price Competition and Patent Term Restoration Act. The seventh, most recent, letter in the series issued July 29, 1988, and provided guidance on the "180-day exclusivity" provision in section 505(j)(4)(B)(iv) of the Federal Food Drug and Cosmetic Act (the Act).

This letter discusses information that the Center for Drug Evaluation and Research, Food and Drug Administration (FDA), believes important to share with generic drug manufacturers and sponsors. The Agency has implemented several changes in response to the events that occurred or were discovered over the past two years. The Office of Generic Drugs has produced a series of Policy and Procedure Guides (the Guides). These Guides should provide you insight into FDA's efforts to devise new policies and procedures that attempt to assure fair, and even-handed dealings with applicants. They seek to make operational FDA's pledge to implement its policies and procedures in an efficient and business-like manner. The list of the Guides that have been issued to date is attached for your reference. FDA will continue to issue Guides in the future, and will provide notice of their availability through Ms. Carolann Hooton, Chief, Freedom of Information Staff, Center for Drug Evaluation and Research (HFD-19), Room 16B-06, 5600 Fishers Lane, Rockville, Maryland 20857. Please contact this office to receive copies.

In April 1989 Robert A. Jerussi, Ph.D., was reassigned to serve as Deputy Director for Chemistry in the Division of Generic Drugs. He is the Agency's lead chemist for issues involving the chemistry and manufacturing control of generic drug products. Among Dr. Jerussi's duties is the quality control of the administrative record including proposed action letters that result from reviews of abbreviated new drug applications (ANDA's) and abbreviated antibiotic drug applications (AADA's). He has identified a need to communicate to industry areas in which we expect regulated industry to change its behavior, and that FDA has changed its administration of the process for reviewing and approving ANDA's.

Examples of the practices that the Agency feels require change on the part of some applicants are:

1. <u>Failure of an Applicant to Provide Complete Submissions.</u> Except as otherwise provided, the Agency will no longer accept an application that is submitted with incomplete or missing data. Examples of what we mean by incomplete or missing data include

at least three months of accelerated stability data, authorization and references to appropriate drug master files, completed batch records for the lots used in generation of stability and bioequivalence studies, properly endorsed 456H forms, complete bioequivalence studies, (or proposed bioequivalence study protocols) and the chemistry, manufacturing, and controls data proposed by the Agency [see proposed rule of July 10, 1989 (54 FR 28872, 28883)]. Further, an application that is accepted but later determined to be deficient will, upon the identification of at least one major defect, be removed from its place in the review process without further substantive review and the sponsor will be so notified. When the identified deficiencies are corrected, and the application is amended, the application will reenter the queue at the appropriate point; i.e., 120 days.

2. Applicant's Inappropriate Use of "Expedited Review Requested" Designation on Some Applications. FDA's regulations, 21 CFR 314.70(b), provide for expedited review of supplemental applications. However, some applicants have abused this provision by requesting expedited review in instances clearly not intended by the regulations. The Agency will review an application designated for an expedited review to determine if it meets the criteria set forth in 21 CFR 314.70(b). Those requests found to meet the criteria will receive expedited review; those found not to meet them will be entered in the queue for regular review. Requests for expedited review for applications that do not meet the criteria are therefore strongly discouraged because the time to consider and reach judgment on the merits of such a request will only delay its entry into the queue.

3. Submission of Incomplete or Erroneous Annual Reports and Implementation of Changes to an Application Without Prior Agency Approval. FDA is obligated to carefully review annual reports. We will especially look for evidence of the following problems that have been frequently identified: (1) omission of stability information the applicant has committed to provide, (2) failure to follow approved stability protocol, or (3) improperly implemented manufacturing changes in the absence of prior approval of supplements.

4. Misrepresentation By the Applicant Regarding Test Data. Each ANDA will be reviewed to determine if an applicant has constructed its application in the absence of a properly manufactured production batch. Such applications will be rejected without substantive review.

5. Attempt by Applicant or its Representative to Defend a Clearly Violative Action or Incorrect Interpretation of the Act or its Regulations. An applicant is expected to understand the Act, its amendments, and implementing regulations. An applicant's submission should relate accurately to the provisions of the Act and the regulations, and the applicant should address completely

and conscientiously the items in a "not approvable" letter.

6. Unprofessional Behavior by Representatives of Applicants Toward Agency Representatives. From time to time an applicant or its representative has behaved in an unprofessional and intimidating manner, including verbal abuse, toward an Agency representative. Such behavior is not acceptable. Similarly, applicants are encouraged to inform FDA if an Agency staff person has treated an applicant or its representative in an unprofessional manner.

The Agency has also identified areas for improvement in its own practices that will have an impact on applicants:

1. At times, FDA has issued conflicting messages on similar application-related issues. Those occurrences may have undermined the confidence that applicants had in the fairness and integrity of the ANDA review process. The Office of Generic Drugs and the Division of Generic Drugs are working to resolve and communicate clear policies on issues that have been identified to us as specific areas of concern such as the size of the bioequivalence batch, the sequence of the various events in the review process, and the operation of the "first in-first reviewed" policy for applications. We will make every effort to improve the consistency of our approach and to resolve such problems. Please call to our attention instances where our instructions appear inconsistent or conflicting.

2. FDA is improving its procedure to adequately document the administrative record. This documentation will provide a clear trail identifying the basis for the Agency's decisions in the evaluation process as required by 21 CFR 10.70.

We seek to build a high quality, efficient generic drug review program. This can be accomplished only by a cooperative effort between the Agency and the generic drugs industry. If applicants understand the process for review of ANDA's, follow the requirements closely for developing ANDA's, and then independently audit them for completeness, quality, organization, and clarity before they are submitted, then this will greatly assist the Agency in efficiently reviewing the applications.

I invite your comments on any of the information contained in this letter. You can direct your comments to me or to the attention of D. Bruce Burlington, M.D., Acting Director, Office of Generic Drugs, Center for Drug Evaluation and Research (HFD-600), Room 13-B-22, Parklawn Building, Rockville, Maryland 20857.

Sincerely yours,

Carl C. Peck, M.D.
Director
Center for Drug Evaluation and Research

Attachment: Policy and Procedure Guides List

June 1990

ATTACHMENT

OFFICE OF GENERIC DRUGS
POLICY AND PROCEDURE GUIDES

The following Office of Generic Drugs Policy and Procedure Guides and miscellaneous documents relating to policy and procedure have been issued.

Guide Number	Date Issued	Subject
1-89	July 13, 1989	Correspondence Practices
2-89	July 13, 1989	Batch Size Requirements for Drug Products Containing Controlled Substances and Inquiries to the Drug Enforcement Administration
3-89	August 1, 1989	Handling Telephone Inquiries on Status of Processing from Applicants or their Representatives
4-89	August 4, 1989	Microbiology Consults
5-89	August 13, 1989	Processing of Supplements That the Applicant Proposes to Put Into Effect Prior to Approval Under 21 CFR 314.70(c).
6-89	August 17, 1989	Not Approvable Actions for ANDA and AADA Supplements
7-89	August 17, 1989	Approvable Actions for ANDA and AADA Supplements
8-89	August 21, 1989	Changes in the Labeling of ANDAs Subsequent to Revision of Innovator Labeling
9-89	August 29, 1989	Providing Copies of Action Documents to Messengers and Other Representatives of ANDA Applicants
10-89	September 21, 1989	Meetings with Pharmaceutical Firm Employees or Their Representatives
11-89	September 25, 1989	Shredding of Carbons and Draft Reviews and Letters

ATTACHMENT (continued)
June 1990

12-89	November 2, 1989	Number of Manufacturing Sites Permitted in an ANDA or AADA
13-89	November 2, 1989	Testing Requirements Applicable to Finished Dosage Forms Manufactured Outside the United States
14-89	November 8, 1989	Signatory Concurrence and Agreement on Final Typed Reviews and Letters and Other Items in the Administrative File
15-90	January 18, 1990	Monitoring and Reporting the Progress of ANDA and AADA Reviews
16-90	March 7, 1990	The "First In-First Reviewed" Policy and Exceptions Thereto as it Applies to Original ANDA's and AADA's and Amendments
17-90	March 29, 1990	Issuance of Action Letters Within the Office of Generic Drugs
18-90	March 29, 1990	Requests for Expedited Review of Supplements to Approved ANDA's and AADA's
19-90	April 12, 1990	Availability of Labeling Guidances
MEMORANDUM:	May 1, 1990	Reviews of ANDAs/AADAs and DMFs
SUPPLEMENT:	May 21, 1990	Supplemental Information on Implementation of the February 1, 1990 Federal Register Notice Regarding FD&C Red #3 (see also March 21, 1990 letter from Daniel L. Michels on this subject - copy attached [to Supplement])
20-90	May 25, 1990	Variations in Solid Oral Dosage Forms and Injectables that can be Included Within a Single ANDA.
21-90	May 22, 1990	The "First In-First Reviewed" Policy and Exceptions Thereto as it Applies to Supplemental Applications to ANDAs and AADAs