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

April 8, 1994

TO ALL ANDA AND AADA APPLICANTS

Dear Sir or Madam:

The purpose of this letter is to provide you with information on a variety of generic drug topics that the Office of Generic Drugs (OGD) believes are important to you and the generic drug industry.

1. INCOMPLETE ABBREVIATED APPLICATIONS

The Office checks abbreviated applications for completeness and acceptability prior to accepting them for review (filing). This letter provides an update of the reasons why the Office refuses to file certain abbreviated applications. This topic was previously discussed in the Office Director's letters to industry dated November 8, 1991, and July 1, 1992.

Attachment A is a checklist of the elements used by the Office for determining if a new abbreviated application is acceptable for filing/receiving. While this checklist doesn't cover all possible filing issues, it provides guidance on the information that is required in a complete application.

The Office continues to refuse to file over 30 percent of applications submitted. Attachment B summarizes the reasons for these actions. The two most frequent reasons for refusing to file/receive applications are: 1) failure to include a letter of authorization from the drug master file (DMF) holder and 2) failure to include a list of convictions required by the Generic Drug Enforcement Act (GDEA). Further information about these two common application omissions is discussed in the following sections:

A. LETTER OF AUTHORIZATION FROM DMF HOLDER

The most frequent reason for an application to be refused for filing is the failure of the applicant to provide an acceptable drug master file (DMF) authorization for the bulk drug. OGD requires authorization to be granted by the holder of the DMF, or its designee, for each source of bulk drug substance. The letter of authorization from the DMF holder must be on the DMF holder's letterhead stationery, signed with an original signature, and dated. The letter must specifically authorize the agency to review the DMF cited by the applicant, and must cite the DMF's holders name, the drug's name, and the DMF number.

Authorization from a third party designee of the DMF holder, such as another corporate entity related to the

DMF holder or a supplier, is not acceptable unless the applicant provides two letters. One letter must be from the DMF holder on the DMF holder's letterhead, signed, and dated. It must specifically grant permission for the third party designee to authorize right of reference to a DMF on the DMF holder's behalf. The second letter must be from the third party, on its letterhead with an original signature and dated. It must refer to the letter of the DMF holder, plus cite the specific applicant, drug name, and DMF number.

B. LIST OF CONVICTIONS UNDER GDEA

The second most frequent reason for refusing to file an application is failure to include a list of convictions of individuals participating in the development of information in the application, as required by the 1992 GDEA. The requirements went into effect on June 1, 1992. In a January 15, 1993, letter to industry, the Office of Generic Drugs stated that, effective February 25, 1993, it would no longer accept for filing abbreviated applications that did not contain the certification and list of convictions required in 21 U.S.C. §335a(k)(1) and (2) of the GDEA.

OGD now requests that the signed certification in the application include not only the list of convictions but also the name(s) of the persons convicted, the title and section of the federal or state statute involved, the sentencing date, the court entering judgment and the case number, if known, and a brief description of the offense. The applicant also should indicate the role of each convicted person in the development or submission of the application, and the time period of the person's involvement in the development of the application.

Beginning June 1, 1994, the Office will no longer accept abbreviated applications for filing that do not contain a signed certification that includes a list of convictions with this additional information. Any questions regarding filing requirements may be directed to the Regulatory Support Branch (301) 594-0315.

2. MULTIPLE SUPPLEMENTS TO THE OFFICE

At times a firm may wish to submit multiple supplements to cover an identical change to several different new drug applications and/or abbreviated applications. To improve the efficiency of the review process, the Center requests that applicants follow these guidelines when this occurs:

A. Prior to sending the multiple supplements, please notify

OGD, and the Offices of Drug Evaluation (ODE) I and/or II, as appropriate. For abbreviated applications, send a copy of the transmittal letter described in item 2.B. by facsimile to the attention of Mr. Robert L. West, OGD, Review Support Branch, (301) 594-0180. For new drug applications, send a copy of the transmittal letter that lists all affected new drug application numbers to Dr. Charles Kumkumian, Assistant Director (Chemistry), ODE I, HFD-102.

B. Send a separate supplement, plus a duplicate copy, for each application affected by the change. Send all the generic supplements in one package to OGD's document control room. Send all the new drug supplements in one package to the appropriate ODE I and/or II Reviewing Divisions. Each package should contain a transmittal letter that provides the date of the supplements, the purpose of the changes, and the file number of each application affected for that Office, i.e., OGD or ODE I/II. Each supplement for a common change should have the same date. Also include the file number of any applications for which similar supplements are being sent to the other Office(s).

Unless the supplements require the review of stability data for approval, OGD intends to assign the review of all the supplements to one chemist. If possible, OGD will coordinate the review of the similar OGD and ODE I/II supplements.

3. ANNUAL REPORTS FOR BULK ANTIBIOTIC DRUGS

Under Section 507 of the Federal Food, Drug, and Cosmetic Act (act), the Office uses an approval mechanism for bulk antibiotic drug substances that is similar to that used to approve antibiotic finished dosage forms. Approval letters issued to all applicants of abbreviated antibiotic drug applications (AADA), including bulk antibiotic drugs, specify that post-marketing reporting requirements are set forth in 21 CFR §314.81. Annual reports must be submitted each year within 60 days of the anniversary date of the approval of the application. However, some bulk substance applicants have not been diligent in submitting these reports. OGD reminds applicants that failure to file the annual reports under section 314.81 and section 507(g) of the act can result in the approval of the application being withdrawn.

Beginning June 1, 1994, all annual reports for bulk AADA's must be accompanied by Form FDA 2252 (Transmittal of Periodic Reports for Drugs for Human Use). The form must be completed and signed with an original signature by the applicant or, if the applicant is not a resident in the United States (U.S.), by the applicant's U.S. agent. The forms are available from

the Consolidated Forms and Publications Distribution Center, Washington Commerce Center, 3222 Hubbard Road, Landover, MD 20785. Form FDA 2252 contains sections which may not be applicable for bulk applications (i.e., nonclinical laboratory studies, clinical data), and these sections can be marked as "not applicable--bulk drug." However, all other sections on this form should be addressed.

4. MINIMUM BATCH SIZE FOR TRANSDERMAL PRODUCTS

The Office has established a tentative policy for a minimum test batch size requirement for transdermal delivery systems. The Office believes this requirement is reasonable based on its discussion with a number of manufacturers with approved abbreviated applications for this dosage form. The test batch size should be at least one tenth of the proposed commercial production batch or 25,000 units for each strength, whichever is greater, all of which are to be fully packaged. OGD will consider, on a case-by-case basis, protocols to package less than the entire test batch.

New biostudies may be required for scale-up beyond ten-fold of the abbreviated application test batches.

5. BIOEQUIVALENCE PROTOCOLS

The Office recommends that before starting bioequivalence studies on a drug product for which a guidance is unavailable, the firm submit the proposed study protocol(s) to the Office. Effective June 1, 1994, protocols submitted for which a bioequivalence guidance exists will not be reviewed unless the proposed protocol differs from the guidance and the cover letter clearly outlines the differences. The protocol should be addressed to the Director, Division of Bioequivalence, for review (21 CFR §320.30) at the address listed in this letter. Protocols submitted for review should be complete and include any supporting references or scientific reprints from the literature which would facilitate the review process.

6. RESEARCH

The Office's research program continues to provide answers to scientific questions and address scientific issues related to the drug approval process. The following is a summary of important initiatives underway or planned in this program.

The results of three extramural contracts with the Universities of Michigan, Uppsala (Sweden), and Maryland were presented at the Generic Drugs Advisory Committee (GDAC) meeting on January 11-12, 1994. The focus of the meeting was

on *in vitro* dissolution. These Universities are conducting the following research on solid, oral immediate-release dosage forms.

A. University of Michigan and University of Uppsala

The fundamental properties which define oral drug bioavailability in humans are solubility and permeability. These properties are being determined at the Universities of Michigan and Uppsala to identify classes of drugs to allow an assessment of the impact of changes in formulation, manufacturing and site on drug product performance. This effort is expected to lead to rational and potentially differing judgments, depending on the drug class, about physicochemical, *in vitro* dissolution and *in vivo* bioequivalence test requirements in the presence of a given change. The drug classification system will be based on *in vitro* and *in vivo* studies of the biopharmaceutical properties of 24 model drugs. All of the drugs being investigated under the manufacturing research contract at the University of Maryland (below) are also being studied under this contract.

B. University of Maryland

Studies involving five model drugs are underway to examine the links between critical manufacturing variables, *in vitro* dissolution, and *in vivo* bioavailability and bioequivalence. This information will assist the Office in better defining minor and major changes in manufacturing and clarifying the role of *in vitro* dissolution in assessing the impact of these changes on bioavailability.

Finally, the agency has awarded three new extramural contracts for FY 1994. The first contract was awarded to the University of Michigan to study the relationship between critical manufacturing variables of topical formulations relative to *in vitro* release characteristics. This study will contribute to a database for the regulatory applications of *in vitro* testing for these formulations. The second contract was awarded to Rutgers University to evaluate experimental variables associated with diffusion cells used to measure *in vitro* drug release from topical dosage forms. The third contract was awarded to the University of Iowa to evaluate the design of histamine challenge studies for documenting the bioequivalence of metered dose inhalers. This information will be considered in the future when the agency evaluates the Office's *Interim Guidance for Documentation of In Vivo Bioequivalence of Albuterol Inhalation Aerosols (Metered Dose Inhalers)* that

issued on January 27, 1994.

7. INDUSTRY COMMENTS TO AUGUST 4, 1993, LETTER TO INDUSTRY

The Office of Generic Drugs (OGD) has received certain questions from generic drug trade associations and others concerning its August 4, 1993, letter to the industry. Due to space restrictions, this section of the letter includes responses to the more significant questions posed, but does not address packaging issues. The Office is preparing a Policy and Procedure Guide on packaging issues and plans to issue it within the next several months.

Q: Specific manufacturing conditions are determined only through experience gained during the validation process, and it is not possible for the initially proposed production batch record to contain more than broad manufacturing ranges and controls. On this basis, can the blank production batch record be submitted with the first annual report? (Section 3, Batch Scale Terminology, August letter.)

A: The proposed production record cannot be submitted in an annual report because the record submitted for the production batch is the basis for evaluation and approval of the initial scale-up proposed in the application. Broad control ranges or undefined conditions, to be established during product manufacture, reduce confidence that the production scale batch is in fact representative of the test batch used to demonstrate bioequivalence. This record must be submitted and identified as the intended scale-up before such evaluation can occur.

OGD's Procedure and Policy Guide (P&PG) 22-90 thus requires that the test batch size be determined based on the proposed production batch. Additionally, 21 CFR §314.94 (58 FR 47352) requires that applications "shall contain the proposed or actual master production record,...to be used for the manufacture of a commercial lot of the drug product."

The purpose of validation with post-approval scale-up is to demonstrate that when the initial in-process controls and specifications which produced the test batch are maintained, the scale-up process reproducibly yields a production batch of equivalent quality.

Q: Can the size of the proposed production batch submitted in the application be changed? (Section 3, Batch Scale Terminology, August letter.)

A: There may be circumstances, prior to approval of the

application, under which the firm wishes to change the size of the proposed production batch. This change can be made by submitting the new proposed production record as an amendment to the application as a replacement for the production batch record originally submitted. Please note, however, that the approved batch record should be the one used to produce the post-approval validation batches.

Q: Is scale-up determined by the size of the final blend, or by the initial quantity of dosage units manufactured from each blend? (Section 6, Common Granulations, August letter.)

A: The test batch size for solid oral dosage forms is based on the quantity of drug product units manufactured. Any scale up considerations also must be determined on this basis. The total amount of in-process granulation may not necessarily correspond to the quantity of an individual strength produced and therefore cannot be used as the basis for scale up.

Q: How are the test batch size requirements of P&PG 22-90 interpreted when the proposed production batch is less than 100,000 units? (Section 3, Batch Scale Terminology, August letter.)

A: For products that are controlled substances (see P&PG #2), products with certain specialized dosage forms, or products that are expected to have extremely low market volume, a firm may wish to propose a production batch size of less than 100,000 dosage units. In these cases, the test batch and proposed production batch must be the same size. Additionally, since the minimum test batch size described by the P&PG is 100,000 dosage units, a rationale to manufacture a smaller batch must be fully justified in a presubmission protocol for acceptance by the Office.

Q: Why should there be a designation in the cover letter that the submission contains sterility assurance data? (Section 8, Microbiological Data, August letter.)

A: This designation will assist the Office in directing the submission to one of OGD's microbiologists for a sterility assurance review. The following information is provided to industry to assist the microbiologist in making the most timely, as well as consistent, review possible. The current reference document is the agency's *Sterility Assurance Guideline* published in the *Federal Register* (58 FR 63996, December 3, 1993). Please present

the appropriate information and data, as outlined in the Guideline, in the Manufacturing and Controls section of the application. The Office further requests that the topics be indexed according to the headings in the Guideline. Stability information requested in the Guideline can be presented with the other stability data, but it should be referenced in the above-mentioned index.

Q: Please clarify the reference in the August 4, 1993, letter to industry that stated, "...the agency...may require the firm to provide dissolution testing data using methods other than those in the USP, especially when an alternative method has been previously approved in the ...application." (Section 10, Dissolution Requirements, August letter.)

A: The Office may approve a dissolution testing method whether or not there is a USP method available at the time the ANDA is approved. If there is a USP method available at the time the ANDA is approved, the Office, according to the statute, may approve an alternative dissolution testing method for valid scientific reasons. The Office, may, in its discretion, determine that the alternative method should be used either instead of or in addition to the USP method. For example, this would occur if the USP method is not discriminating or uses hydro-alcoholic (or organic solvent) medium for dissolution testing. The Office expects that instances will occur only rarely where dissolution tests and specifications that differ from the USP method will be proposed.

If no USP method is available at the time the ANDA is approved, the dissolution testing method approved is generally, but not restricted to, the one used by the innovator. The Office may approve a dissolution testing method developed by the agency for the specific drug product. Subsequent to approval, if the USP establishes a dissolution testing method, acceptable to the agency, the firm must conduct post-approval quality control testing using this USP method.

8. REQUESTS FOR DEVIATION FROM OGD POLICY

Applicants are encouraged to follow the policies and procedures published in the regulations, Center Guidelines, and OGD Policy and Procedure Guides. However, requests for information about deviations from Office policies can arise before or after an abbreviated application is submitted. Before an application is submitted, questions about deviating from the Office's policies and procedures should be directed to the Acting Director, OGD. After an application is

submitted, such questions that are specific to an application should be resolved through the routine application review process.

Regardless of whether the question arises before or after an application is submitted, the requester should provide the following information in the opening statement of the letter:

A. Indicate whether the request is a general question or applies specifically to an individual or class of applications and provide the application numbers, as appropriate.

B. Indicate the nature of the request, and provide a reference to the appropriate guideline, policy or regulation in question, clearly stating the deviation about which information is requested and/or question about the issue.

C. Indicate the applicable dosage forms and strengths.

If the inquiry about a deviation from Office policy relates to a packaging issue, please follow the procedures stated below:

A. If the application has been submitted and the inquiry pertains to the mechanism by which the firm is to initiate a change in the container/closure system, the firm should include the type of dosage form and information on the approved and proposed packaging components including supplier, composition, drawings and any additional testing such as incoming release testing.

The Office then will be able to determine whether the change can be submitted as a supplement or in the annual report. The Office, if requested, will provide the applicant with a list of information which should be submitted to support the change.

B. If the application has not yet been submitted and the request is for waiver of batch packaging requirements, an applicant should provide a protocol that demonstrates that the test batch is chemically, physically and microbiologically uniform. Adequate controls should be proposed.

The protocol should provide at least the following:

(1) a description of the dosage form and its properties, including any characteristics that may be affected by environmental factors, such as heat, light, humidity and oxygen,

(2) a description of the container/closure system and packaging and labeling operations, and

(3) a description of the sampling plan and analytical methodology.

Once a written response is provided by the Office, please include a copy of the response in the ANDA/AADA submission(s).

9. OFFICE PERSONNEL FOR QUESTIONS

From time to time, individuals outside the agency call several members of the Office requesting the same information. To conserve valuable Office time and resources and assure that the opinions provided to the public are uniform, the Office requests that questions be directed to the following individuals, depending on the content of the question:

A. Questions about the chemistry review status of an application should be directed to the Branch consumer safety officer (CSO), if known, or the Regulatory Support Branch, (301) 594-0315,

B. Questions about the bioequivalence review status should be directed to Dr. Jason Gross, (301) 594-0315,

C. Labeling questions should be directed to Mr. Jerry Phillips, Chief, Labeling Review Branch, (301) 594-0365, or

D. General information should be directed to the Regulatory Support Branch (301) 594-0315, unless stated otherwise in this letter.

10. MAILING ADDRESS AND TELEPHONE NUMBERS

The Office continues to get several inquiries for the following information:

A. Submissions and other correspondence intended to be part of an abbreviated application, whether sent by the U. S. Mail, a courier service or by a parcel service should be addressed as follows:

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

B. Correspondence not associated with an abbreviated application should include the above address and also

include the name of the person to whom the correspondence is directed.

C. The Office has new telephone numbers. Generally you can replace the numbers 295-8xxx with 594-0xxx and proceed. For example, the number 295-8340 has been changed to 594-0340. A few new numbers do not follow this rule, but if you have questions, please call the Regulatory Support Branch (301) 594-0315.

The Office of Generic Drugs appreciates your consideration of the issues raised in this letter. Your attention to these matters will assist us in our efforts to improve the generic drugs review process.

Sincerely yours,

Douglas L. Sporn

Douglas L. Sporn
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

indusltr.04

CHECKLIST FOR COMPLETENESS AND ACCEPTABILITY FOR FILING
ABBREVIATED APPLICATIONS

	Yes	No
Regulatory and Administrative Requirements		
- Methods Validation package (if non-USP drug product) (3 copies)		
- Cover Letter		
- Letters of Authorization		
U.S. Agent (If Needed, Countersignature on 356h)		
DMF Referral and Authorizations		
- 356h Form - Completed/Original Signature		
- Table of Contents		
- Listed Drug or		
AADA Monograph (if appropriate)		
- Information to show proposed product is the same as the listed product: (i)(a) indications (ii) active ingredient(s) (iii) (a) route (b) dosage form (c) strength (iv) labeling -- side by side comparison of insert labeling and container labels.		
- Formulation for:		
Ophthalmics/Otics/Externals/Parenterals		
+ Meet requirements per 21 CFR 314.94?		
+ Characterize and explain differences as required		
Parenterals: Same Size Container (strength/volume)		
Petition Required		
Debarment Certification with original signature . . .		
- List of Convictions with signature		
- Third Copy Certification with original signature. . . .		
- Patent Certification with signature		
Use Patent Statement? (if required)		
If so, exclude Use in labeling/indications?		
- Exclusivity Addressed		
- Labeling: 4 copies of draft ( ) or 12 copies of FPL( )		
- Environmental Assessment		
Compliance Statement		
- Statement re Rx/OTC Status		
Chemistry, Manufacturing and Controls Information		
- Components & Composition of the drug product		
- Batch Formulation		
- Manufacturing Procedures (Executed Batch Records for exhibit batch)		
- Package entire exhibit batch		
- Master Production Batch Record for largest batch size intended for production. (No more than 10x pilot batch)		
Certification of cGMPs.		
Description of Facility (or Type II DMF reference?)		
- Address of Manufacturing Site for Exhibit/Production Batches		
- If sterile product, information provided for Aseptic Procedures___ Terminal Sterilization Procedures___		

ATTACHMENT A (CONTINUED)

	Yes	No
Specifications and Tests for Active Ingredient and Dosage Form		
Source of Active Ingredient		
Cert. of Analysis from Manufacturer of Active Ingredient		
Applicant Cert. of Analysis For Active Ingredient		
Cert. of Analysis for finished product		
- Specifications and Tests for Inactive Ingredients		
Source of Inactive Ingredients		
Cert. of Analysis from Manufacturer of Inactive Ingredient		
- Stability Profile Including Stability Data		
3 months Accelerated Stability Data		
Batch Numbers Listed on Stability Records		
Samples Statement Plus Data		
Bioequivalence Information		
- Bioavailability/Bioequivalence		
Completed Study(ies) results		
In Vivo Study/Waiver Request		
Comparative Dissolution Data		

ATTACHMENT A (CONTINUED)

	Yes	No
Specifications and Tests for Active Ingredient and Dosage Form		
Source of Active Ingredient		
Cert. of Analysis from Manufacturer of Active Ingredient		
Applicant Cert. of Analysis For Active Ingredient		
Cert. of Analysis for finished product		
- Specifications and Tests for Inactive Ingredients		
Source of Inactive Ingredients		
Cert. of Analysis from Manufacturer of Inactive Ingredient		
- Stability Profile Including Stability Data		
3 months Accelerated Stability Data		
Batch Numbers Listed on Stability Records		
Samples Statement Plus Data		
Bioequivalence Information		
- Bioavailability/Bioequivalence		
Completed Study(ies) results		
In Vivo Study/Waiver Request		
Comparative Dissolution Data		

REFUSAL TO FILE LETTERS BY REASON AND FREQUENCY
JANUARY 1, 1993, to DECEMBER 31, 1993

REASON	FREQUENCY
NO AUTHORIZATION OF THE DMF	15
NO CONVICTION STATEMENT	14
NO ENVIRONMENTAL IMPACT ANALYSIS	9
INCOMPLETE 356h	9
NO DEBARMENT CERTIFICATION	9
FAILURE TO IDENTIFY & CHARACTERIZE THE DIFFERENCES IN THE INACTIVE INGREDIENTS	9
NO MASTER PRODUCTION RECORD	9
NO AUTHORIZATION OF AGENT	8
NO SIDE-BY-SIDE COMPARISON OF LABELING	8
NONCOMPLIANCE WITH ANDA PPG #20-90	8
INCOMPLETE BATCH RECORDS	8
NEED FOUR COPIES OF DRAFT LABELING	7
NO COMPARATIVE DISSOLUTION DATA	6
NO CGMP CERTIFICATION STATEMENT	5
INCOMPLETE ENGLISH TRANSLATION	5
NO REFERENCE BULK DRUG	4
IMPROPER PATENT CERTIFICATION	4
NO INFO ON CONTAINER CLOSURE	4
NO CERT. OF ANALYSIS FOR THE LOTS OF INTERMEDIATE DRUG SUBSTANCE	4
EXCLUSIVITY RIGHTS NOT ADDRESSED	3
NEED OF DESI UPGRADE NOTICE	3
FAILURE TO IDENTIFY SOURCE OF MICROORGANISM	3
LOT NUMBERS OF STABILITY STUDIES DO NOT CORRESPOND WITH BATCH RECORD	3
STRENGTH NOT EQUIVALENT TO ANY LISTED DRUG PRODUCT	2
NO CERTIFICATION OF FIELD COPY	2
NO DESCRIPTION OF FOREIGN MANUFACTURING FACILITIES PER PPG #26-80	2
GROSSLY INCOMPLETE SUBMISSION	2
UNAPPROVABLE AS AN ANDA/AADA	2
NO CERTIFICATE OF ANALYSIS OF INACTIVE INGREDIENTS	1

ATTACHMENT B (CONTINUED)

REASON	FREQUENCY
BATCH RECORD FOR THE WRONG STRENGTH	1
NO COPY OF PETITION	1
NO SAMPLE STATEMENT	1
NO RECORD OF PACKAGING THE EXHIBIT BATCH	1
NO COMPLETED BATCH RECORD	1
INCOMPLETE STABILITY DATA	1
NO CERTIFICATE OF ANALYSIS FOR BATCH USED IN THE STABILITY STUDY	1
FAILURE TO PROVIDE SUFFICIENT BATCH QUANTITY	1
NO IN-VIVO BIO STUDY	1
INCORRECT LISTED DRUG CITED	1
TOTAL	**178**

NUMBER OF REASONS CITED IN A REFUSE TO FILE LETTER
JANUARY 1, 1993 to DECEMBER 31, 1993

REASONS CITED	LETTERS ISSUED
ONE	38
TWO	15
THREE	4
FOUR	7
FIVE	2
SIX	1
SEVEN	2
EIGHT	5
TOTAL	74