NDA 88-482

Sidmak Laboratories, Inc.
Attention: Satish Patel, Ph.D.
17 West Street
P.O. Box 371
East Hanover, NJ 07936

Gentlemen:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for Disulfiram Tablets, 250 mg.

Reference is also made to your communication dated December 2, 1983.

We have completed the review of this abbreviated new drug application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved.

Any significant change in the conditions outlined in this abbreviated new drug application requires an approved supplemental application before the change may be made, except for changes made in conformance with other provisions of Section 314.8 of the new drug regulations.

This Administration should be advised of any change in the marketing status of this drug.

The requirement for adequate data to assure the biologic availability is being deferred at the present time. However, our action in approving this application is based upon an understanding that if this requirement is reinstated you will perform the appropriate procedures.

For Initial Campaigns: We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your immediate advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Advertising and Labeling (HFN-240). Also, please do not use Form FD-2253 for this submission.

For Subsequent Campaigns: We call your attention to Regulation 21 CFR 310.300(b)(3) which requires that all material for any subsequent advertising or promotional campaigns at the time of their initial use be submitted to our Division of Drug Advertising and Labeling (HFN-240) with a completed Form FD-2253. A copy of Form FD-2253 is enclosed for your convenience.

The enclosures summarize the conditions relating to the approval of this application.

Sincerely yours,

Marvin Seife

12/8/83

Marvin Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
National Center for Drugs and Biologics

Enclosures:
Conditions of Approval of a New Drug Application
Records & Reports Requirements
Form FD 2253

cc: NWK-DO
HFN-530
HFN-5
HFN-313
HFN-616
KJohnson/JMeyer/CChang
R/D INITIAL JMeyer/MSeife
mm:12/7/83 (3437c)
Approval

12-7-83

12-7-83

for J.L.
12-7-83

NOTICE OF APPROVAL
NEW DRUG APPLICATION OR SUPPLEMENT

NDA NUMBER: 88-482

DATE APPROVAL LETTER ISSUED:

TO: Press Relations Staff (HFI-40)

FROM: [XX] Bureau of Drugs [ ] Bureau of Veterinary Medicine

ATTENTION

Forward original of this form for publication only after approval letter has been issued and the date of approval has been entered above.

TYPE OF APPLICATION: [ ] ORIGINAL NDA [ ] SUPPLEMENT TO NDA [X] ABBREVIATED ORIGINAL NDA [ ] SUPPLEMENT TO ANDA

CATEGORY: [X] HUMAN [ ] VETERINARY

TRADE NAME (or other designated name) AND ESTABLISHED OR NONPROPRIETARY NAME (if any) OF DRUG:

Disulfiram

DOSAGE FORM: Tablets

HOW DISPENSED: [X] RX [ ] OTC

ACTIVE INGREDIENT(S) (as declared on label. List by established or nonproprietary name(s) and include amount(s), if amount is declared on label.)

Disulfiram 250 mg

NAME OF APPLICANT (Include City and State)

Sidmak Laboratories, Inc.
East Hanover, NJ 07936

PRINCIPAL INDICATION OR PHARMACOLOGICAL CATEGORY

Alcohol deterrent, antabuse

COMPLETE FOR VETERINARY ONLY

ANIMAL SPECIES FOR WHICH APPROVED

COMPLETE FOR SUPPLEMENT ONLY

CHANGE APPROVED TO PROVIDE FOR

FORM PREPARED BY

NAME: C. Chang

DATE: 12-7-83

FORM APPROVED BY

NAME: J. Meyer

DATE:

FORM FD 1642 (2/75) PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED.

ABBREVIATED NEW DRUG APPLICATION OR SUPPLEMENT	STATEMENT DATE: DES: 7888	NDA NUMBER: 88-482

NAME AND ADDRESS OF APPLICANT

ak Laboratories, Inc.
East Hanover, NJ 07936

ORIGINAL
AMENDMENT X
SUPPLEMENT
RESUBMISSION X
CORRESPONDENCE
REPORT
OTHER

PURPOSE OF AMENDMENT

labeling information

DATE(S) OF SUBMISSION(S)

As per letter

PHARMACOLOGICAL CATEGORY	NAME OF DRUG	HOW DISPENSED
lcohol deterrent ntabuse	Disulfiram	RX X OTC
OSAGE FORM(S)	POTENCY(IES)	RELATED IND/NDA/DMF
blets	250 mg	88-483 500 mg 88-482 250 mg
TERILIZATION	SAMPLES	
/A	N/A (USP)	

ABELING

ntisfactory per K. Johnson

OLOGIC AVAILABILITY

ed dissolution per Dr. Dighe on 9-6-83

TABLISHMENT INSPECTION

quested

PONENTS, COMPOSITION, MANUFACTURING, CONTROLS

e issued letter

KAGING

te opaque H.D. polyethylene bottles and metal cap, inner form seal

ILITY

otocol: See issued letter

p. Date: Firm request for 2 yrs.

RKS AND
LUSIONS: Approval

C. Chang

12-7-83

NDC 50111-331-01

Disulfiram Tablets USP 250mg

Each tablet contains:
Disulfiram USP 250mg

CAUTION: Federal (USA) law prohibits dispensing without prescription

100 Tablets

Usual dosage and complete prescribing information: See accompanying literature.

DEC 8 1983

Store at controlled room temperature 15° to 30°C (59° to 86°F).

This is a bulk package. Dispense contents with child-resistant closure (as required) and in tight, light resistant container as defined in the USP/NF.

Keep tightly closed.

Keep this and all medication out of the reach of children.

Gidmak®
LABORATORIES, INC.
17 West Street
East Hanover, NJ 07936

Control No:
Exp. Date:

NDC 50111-331-03

Disulfiram Tablets USP 250mg

Each tablet contains:
Disulfiram USP .... 250mg.

CAUTION: Federal (USA) law prohibits dispensing without prescription

1000 Tablets

Usual dosage and complete prescribing information: See accompanying literature.

APPROVED
DEC 8 1983

Store at controlled room temperature 15° to 30°C (59° to 86°F).

This is a bulk package. Dispense contents with child-resistant closure (as required) and in tight, light resistant container as defined in the USP/NF.

Keep tightly closed.

Keep this and all medication out of the reach of children.

Gidmak®
LABORATORIES, INC.
17 West Street
East Hanover, NJ 07936

Control No:
Exp. Date:

DURATION OF THERAPY: The daily, uninterrupted administration of Disulfiram must be continued until the patient is fully recovered socially and a basis for permanent self-control is established. Depending on the individual patient, maintenance therapy may be required for months or even years.

TRIAL WITH ALCOHOL: During early experience with Disulfiram, it was thought advisable for each patient to have at least one supervised alcohol-drug reaction. More recently, the test reaction has been largely abandoned. Furthermore, it should never be administered to a patient over 50 years of age. A clear, detailed, and convincing description of the reaction is felt to be sufficient in most cases.

However, where a test reaction is deemed necessary, the suggested procedure is as follows:

After the first one to two weeks' therapy with 500 mg. daily, a drink of 15 cc (½ oz.) of 100 proof whiskey or equivalent is taken slowly. This test dose of alcoholic beverage may be repeated once only so that the total dose does not exceed 30 cc. (1 oz.) of whiskey. Once a reaction develops, no more alcohol should be consumed. Such tests should be carried out only when the patient is hospitalized, or comparable supervision of facilities, including oxygen, are available.

MANAGEMENT OF DISULFIRAM-ALCOHOL REACTION: In severe reactions, whether caused by an excessive test dose or by the patient's unsupervised ingestion of alcohol, supportive measures to restore blood pressure and treat shock should be instituted. Other recommendations include: oxygen, carbogen (95 per cent oxygen and 5 per cent carbon dioxide), vitamin C intravenously in massive doses (1 Gm.) and ephedrine sulfate. Antihistamines have also been used intravenously. Potassium levels should be monitored particularly in patients on digitalis since hypokaliemia has been reported.

HOW SUPPLIED: As white, round, unscored, compressed tablet, impressed with SL 331, containing 250 mg. of Disulfiram, in bottles of 100 and 1000 tablets.

NDC #50111-331-01, bottle of 100 tablets
NDC #50111-331-02, bottle of 500 tablets

As white, round, unscored, compressed tablet, impressed with SL 332, containing 500 mg. of Disulfiram, in bottles of 100 and 500 tablets.

NDC #50111-332-01, bottle of 100 tablets
NDC #50111-332-03, bottle of 1000 tablets

Manufactured by
SIDMAK LABORATORIES, INC.
17 West St.
East Hanover, N.J. 07936

Revised: 11/83

DISULFIRAM TABLETS USP

50111-331
50111-332

CAUTION: Federal law prohibits dispensing without prescription.

WARNING: Disulfiram should *never* be administered to a patient when he is in a state of alcohol intoxication or without his full knowledge.

The physician should instruct relatives accordingly.

DESCRIPTION: CHEMICAL NAME: bis(diethylthiocarbamoyl) disulfide
STRUCTURAL FORMULA:

$$(C_2H_5)_2NC(=S)-S-S-C(=S)N(C_2H_5)_2$$

Disulfiram occurs as a while to offwhite, odorless, and almost tasteless powder, soluble in water to the extent of about 20 mg. in 100 ml., and in alcohol to the extent of about 3.8 Gm. in 100 ml.

ACTION: Disulfiram produces a sensitivity to alcohol which results in a highly unpleasant reaction when the patient under treatment ingests even small amounts of alcohol.

Disulfiram blocks the oxidation of alcohol at the acetaldehyde stage. During alcohol metabolism after Disulfiram intake, the concentration of acetaldehyde occurring in the blood may be 5 to 10 times higher than that found during metabolism of the same amount of alcohol alone.

Accumulation of acetaldehyde in the blood produces the complex of highly unpleasant symptoms referred to hereinafter as the Disulfiram-alcohol reaction. This reaction which is proportional to the dosage of both Disulfiram and alcohol, will persist as long as alcohol is being metabolized. Disulfiram does not appear to influence the rate of alcohol elimination from the body.

Disulfiram is slowly absorbed from the gastrointestinal tract and is slowly eliminated from the body. One (or even two) weeks after a patient has taken his last dose of Disulfiram, ingestion of alcohol may produce unpleasant symptoms.

Prolonged administration of Disulfiram does not produce tolerance; the longer a patient remains on therapy, the more exquisitely sensitive he becomes to alcohol.

INDICATIONS: Disulfiram is an aid in the management of selected chronic alcohol patients who *want* to remain in a state of enforced sobriety so that supportive and psychotherapeutic treatment may be applied to best advantage. (Used alone, without proper motivation and without supportive therapy, Disulfiram is not a cure for alcoholism, and it is unlikely that it will have more than a brief effect on the drinking pattern of the chronic alcoholic.)

CONTRAINDICATIONS: Patients who are receiving or have recently received metronidazole, paraldehyde, alcohol, or alcohol-containing preparations, e.g. cough syrups, tonics, and the like should not be given Disulfiram.

Disulfiram is contraindicated in the presence of severe myocardial disease or coronary occlusion, psychoses, or hypersensitivity.

WARNINGS:

Disulfiram should *never* be administered to a patient when he is in a state of alcohol intoxication or without his full knowledge

The physicians should instruct relatives accordingly.

The patient must be fully informed of the Disulfiram-alcohol reaction. He must be strongly cautioned against surreptitious drinking while taking the drug, and he must be fully aware of possible consequences. He should be warned to avoid possible consequences. He should be warned to avoid alcohol in disguised forms, i.e. in sauces, vinegars, cough mixtures, and even aftershave lotions and back rubs. He should also be warned that reactions may occur with alcohol up to 14 days after ingesting Disulfiram.

THE DISULFIRAM-ALCOHOL REACTION: Disulfiram plus alcohol, even small amounts, produce flushing, throbbing in head and neck, throbbing headache, respiratory difficulty, nausea, copious vomiting, sweating, thirst, chest pain, palpitation, dyspnea, hyperventilation, tachycardia, hypotension, syncope, marked uneasiness, weakness, vertigo, blurred vision, and confusion. In severe reactions there may be respiratory depression, cardiovascular collapse, arrhythmias, myocardial infarction, acute congestive heart failure, unconsciousness, convulsions, and death.

The intensity of the reaction varies with each individual, but in generally proportional to the amounts of Disulfiram and alcohol ingested. Mild reactions may occur in the sensitive individual when the blood alcohol concentration is increased to as little as 5 to 10 mg. per 100 cc. Symptoms are fully developed at 50 mg. per 100 cc., and unconsciousness usually results when the blood alcohol level reaches 125 to 150 mg.

The duration of the reaction varies from 30 to 60 minutes to several hours in the more severe cases, or as long as there is alcohol in the blood.

DRUG INTERACTIONS: Disulfiram appears to decrease the rate at which certain drugs are metabolized and so may increase the blood levels and the possibility of clinical toxicity of drugs given concomitantly.

Disulfiram should be used with caution in those patients receiving diphenylhydantoin and its congeners, since toxic levels of these antiepileptic agents have been reported during concomitant disulfiram therapy.

It may be necessary to adjust the dosage of oral anticoagulants upon beginning or stopping disulfiram, since disulfiram may prolong prothrombin time.

Patients taking isoniazid when disulfiram is given should be observed for the appearance of unsteady gait or marked changes in mental status and the disulfiram discontinued if such signs appear.

CONCOMITANT CONDITIONS: Because of the possibility of an accidental Disulfiram-alcohol reaction, Disulfiram should be used with extreme caution in patients with any of the following conditions: diabetes mellitus, hypothyroidism, epilepsy, cerebral damage, chronic and acute nephritis, hepatic cirrhosis or insufficiency.

USAGE IN PREGNANCY: The safe use of this drug in pregnancy has not been established. Therefore, Disulfiram should be used during pregnancy only when, in the judgement of the physician, the probable benefits outweigh the possible risks.

PRECAUTIONS: It is suggested that every patient under treatment carry an *Identification Card*, stating that he is receiving Disulfiram and describing the symptoms most likely to occur as a result of the Disulfiram-alcohol reaction. In addition, this card should indicate the physician or institution to be contacted in emergency.

Alcoholism may accompany or be followed by dependence on narcotics or sedatives. Barbiturates have been administered concurrently with Disulfiram without untoward effects, but the possibility of initiating a new abuse should be considered.

Base line and follow-up transaminases tests (10-14 days) are suggested to detect any hepatic dysfunction that may result with Disulfiram therapy.

ADVERSE REACTIONS: (See Contraindications, Warnings, and Precautions.)

Occasional skin eruptions are, as a rule, readily controlled by concomitant administration of an antihistaminic drug.

In a small number of patients, a transient mild drowsiness, fatigue impotence, headache, acneform eruptions, allergic dermatitis, or a metallic or garlic-like aftertaste may be experienced during the first two weeks of therapy. These complaints usually disappear spontaneously with the continuation of therapy or with reduced dosage.

Psychotic reactions have been noted, attributable in most cases to high dosage, combined toxicity (with metronidazole or isomizid), or to the unmasking of underlying psychoses in patients stressed by the withdrawal of alcohol.

There have been reports of polyneuritis and peripheral neuritis, and rare instances of optic neuritis. One case of cholestatic hepatitis has been reported, but its relationship to Disulfiram has not been unequivocally established.

DOSAGE AND ADMINISTRATION: Disulfiram should never be administered until the patient has abstained from alcohol for at least 12 hours.

INITIAL DOSAGE SCHEDULE: In the first phase of treatment, a *maximum* of 500 mg. daily is given in a single dose for one to two weeks. Although usually taken in the morning, Disulfiram may be taken on retiring by patients who experience a sedative effect. Alternatively, to minimize, or eliminate, the sedative effect, dosage may be adjusted downward.

MAINTENANCE REGIMEN: The average maintenance dose is 250 mg. daily (range, 125 to 500 mg.), it should not exceed 500 mg. daily.

NOTE: Occasional patients, while seemingly on adequate maintenance doses of Disulfiram, report that they are able to drink alcoholic beverages with impunity and without any symptomatology. All appearances to the contrary, such patients must be presumed to be disposing of their tablets in some manner without actually taking them. Until such patients have been observed reliably taking their daily Disulfiram tablets (preferably crushed and well mixed with liquid), it cannot be concluded that Disulfiram is ineffective.

NDA 88-482

Sidmak Laboratories, Inc.
Attention: Satish Patel, Ph.D.
17 West Street
P.O. Box 371
East Hanover, NJ 07936

Gentlemen:

Please refer to your new drug application submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for Disulfiram Tablets, 250 mg.

Reference is also made to your communication dated November 14, 1983.

The application is deficient and therefore not approvable under Section 505(b) of the Act as follows:

It fails to include 12 copies of the final printed labeling identical in content to the draft copies.

The file is now closed. If you wish to reopen it, the submission should be in the form of an amendment to this application, adequately organized, which represents the information necessary to remove all deficiencies we have outlined.

If you do not agree with our conclusions, you may make a written request to file the application over protest, as authorized by 21 CFR 314.110(d). If you do so, the application shall be re-evaluated and within 90 days of the date of receipt of such request (or additional period as we may agree upon), the application shall be approved or you shall be given a written notice of opportunity for a hearing on the question of whether the application is approvable.

Sincerely yours,

for 11-29-83

Marvin Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
National Center for Drugs and Biologics

cc: NWK-DO 11/28/83
HFN-530
JMeyer/CChar 11-28-83
R/D INITIAL JMeyer/MSeife
mm:11/22/83 (3006c)
Not Approvable
11/28/83

CHEMIST'S REVIEW FOR ABBREVIATED NEW DRUG APPLICATION OR SUPPLEMENT

STATEMENT DATE:

DES: 7888

NDA NUMBER:

88-482

NAME AND ADDRESS OF APPLICANT

Sidmak Laboratories, Inc.
East Hanover, NJ 07936

ORIGINAL
AMENDMENT X
SUPPLEMENT
RESUBMISSION X
CORRESPONDENCE
REPORT
OTHER

PURPOSE OF AMENDMENT

Control and labeling information

DATE(S) OF SUBMISSION(S)

As per letter

PHARMACOLOGICAL CATEGORY

Alcohol deterrent
Antabuse

NAME OF DRUG

Disulfiram

HOW DISPENSED

RX X OTC

DOSAGE FORM(S)

Tablets

POTENCY(IES)

250 mg

RELATED IND/NDA/DMF

88-483 500 mg
88-482 250 mg

STERILIZATION

N/A

SAMPLES

N/A (USP)

LABELING

Satisfactory per K. Johnson, need FPL

BIOLOGIC AVAILABILITY

Need dissolution per Dr. Dighe on 9-6-83

ESTABLISHMENT INSPECTION

Requested

COMPONENTS, COMPOSITION, MANUFACTURING, CONTROLS

See issued letter

PACKAGING

Late opaque H.D. polyethylene bottles and metal cap, inner form seal

STABILITY

Protocol: See issued letter

Exp. Date: Firm request for 2 yrs.

REMARKS AND CONCLUSIONS: Not approvable

C. Chang 11-28-83

NDA 88-482

Sidmak Laboratories, Incorporated
Attention: Satish P. Patel, Ph.D.
P.O. Box 371
East Hanover, New Jersey 07936

Gentlemen:

Reference is made to the dissolution data you submitted on October 25, 1983 for Disulfiram Tablets, 250 mg.

The data have been reviewed by our Division of Biopharmaceutics and they have the following comments:

> "Due to the low solubility of disulfiram, the Division of Biopharmaceutics has deferred the in vitro dissolution requirements for this product. When an appropriate dissolution methodology becomes available, the firm will be expected to comply with requirements."

Sincerely yours,

Marvin Seife 11/18/83

Marvin Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
National Center for Drugs and Biologics

cc: NWK-DO
HFN-530
MSeife/mstephens: 11/17/83 (2906c)

Generic Name: Disulfiram

Trade Name:

Dosage: 250 mg Tablets

ANDA #: 88-482

Reviewer: L.A. Ouderkirk

Firm Name: Sidmak Laboratories, Inc

Firm Location: East Hanover, New Jersey

Submission Date: October 25, 1983

NOV 17 1983

Wang # 2704e

REVIEW OF DISSOLUTION DATA

Objective of Submission: Comparative dissolution data in three media are submitted for ANDA approval.

Condition for Dissolution Testing

USP XX Apparatus Paddle X Basket ____ RPM 50

Medium: H_2O/0.1N HCl/SIF Volume 900 ml

Number of Tab/Capsules Tested: 12

Reference Drug: Antabuse® 250 mg Tablets (Ayerst)

Assay Methodology

Dissolution Requirement

USP Final _____ USP Proposed _____

FDA Standard _____ FDA Bioequivalence Standard _____

Comparative X _____ Individual _____

Results

	Time	Sidmak Test Product Lot No 83-048-T Mean % Dissolved	Range, (CV)	Antabuse® (Ayerst) Reference Product Lot No. 1BQ1 Mean % Dissolved	Range, (CV)
Water	15	1.11	(4.4)	0.68	(46.5)
	30	1.72	(2.7)	1.01	(55.9)
	45	2.02	(1.8)	1.28	(39.5)
	60	2.27	(1.3)	1.78	(36.2)
0.1N HCl	15	0.72	(2.9)	0.88	(23.2)
	30	1.24	(4.5)	1.43	(10.8)
	45	1.59	(4.7)	1.70	(7.5)
	60	1.84	(2.7)	1.80	(5.0)
SIF	15	0.81	(4.8)	0.43	(32.7)
	30	1.17	(3.0)	0.72	(43.1)
	45	1.43	(2.7)	0.92	(41.1)
	60	1.61	(3.7)	1.10	(36.8)

Comments:

1. Due to the low solubility of disulfiram, the Division of Biopharmaceutics has deferred the in vitro dissolution requirements for this product. When an appropriate dissolution methodology becomes available, the firm will be expected to comply with requirements.

Recommendations:

1. The firm should be informed of Comment # 1, above.

2. From the biopharmaceutics point of view, the application is approvable.

11-9-83

Larry A. Ouderkirk, Biologist
Biopharmaceutics Review Branch

Initialed by C.M. Ise

cc: ANDA # 88-482 orig., HFN-530 (4), HFN-522 (Ouderkirk, Ise - 2), HFN-503 (Hare), Chron File, Drug File, Review File, Division File

LAO/crt/Wang # 2704e/11/08/83

NDA 88-482

Sidmak Laboratories, Inc.
Attention: Satish Patel, Ph.D.
17 West Street
P.O. Box 371
East Hanover, New Jersey 07936

Gentlemen:

Please refer to your new drug application submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for Disulfiram Tablets, 250 mg.

Reference is also made to your communication dated October 25, 1983, for ANDA 88-483.

The application is deficient and therefore not approvable under Section 505(b) of the Act as follows:

1. Other information requested per our letter of October 24, 1983.

2. The submitted dissolution data for ANDA 88-483 has been referred to our Division of Biopharmaceutics. We will correspond with you further when their results become available.

The file is now closed. If you wish to reopen it, the submission should be in the form of an amendment to this application, adequately organized, which represents the information necessary to remove all deficiencies we have outlined.

If you do not agree with our conclusions, you may make a written request to file the application over protest, as authorized by 21 CFR 314.110(d). If you do so , the application shall be re-evaluated and within 90 days of the date of receipt of such request (or additional period as we may agree upon), the application shall be approved or you shall be given a written notice of opportunity for a hearing on the question of whether the application is approvable.

Sincerely yours,

11/2/83

11/3/83

Harvin Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
National Center for Drugs and Biologics

cc: NDA-88
HFN-530
JMeyer/CChang 11-2-83
R/D INITIAL JMeyer/MSeife
mm:11/2/83 (2414c)
Not approvable

ABBREVIATED NEW DRUG APPLICATION OR SUPPLEMENT | Statement Date: DES: 7888 | NDA # 88-482

NAME AND ADDRESS OF APPLICANT:

Sidmak Laboratories, Inc.
East Hanover, NJ 07936

ORIGINAL
AMENDMENT X
SUPPLEMENT
RESUBMISSION
CORRESPONDENCE X
REPORT
OTHER

PURPOSE OF AMENDMENT/SUPPLEMENT

Dissolution data

DATE(s) OF SUBMISSION(S)

As per letter

PHARMACOLOGICAL CATEGORY	NAME OF DRUG
Alcohol deterrent Antabuse	Disulfiram

DOSAGE FORM	POTENCY(IES)
Tablets	250 mg

STERILIZATION	SAMPLES
A	NA (USP)

PROPOSED
RX X OTC

RELATED IND/NDA/DMF

88-483 500 mg
88-482 250 mg

LABELING

Unsatisfactory per K. Johnson

BIOBIOAVAILABILITY

Need dissolution per Dr. Dighe on 9-6-83

ESTABLISHMENT INSPECTION

Requested

COMPONENTS, COMPOSITION, MANUFACTURING, CONTROLS

See issued letter

PACKAGING

White opaque H.D. polyethylene bottles and metal cap, inner form seal

STABILITY:

Protocol: See issued letter

Exp. Date: Firm request for 2 yrs.

REMARKS & CONCLUSION:

Approvable

H. Chang 11-2-83

idmak
LABORATORIES, INC.

17 WEST STREET • P.O. BOX 371 • EAST HANOVER, NJ 07936 • TELEPHONE: (201) 386-5566

Drug in Bio

October 25, 1983

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of the Associate Director for Drug Monographs
Office of Drugs
National Center for Drugs & Biologics
5600 Fishers Lane
Rockville, MD 20852

ORIG NEW CORRES

BIOAVAILABILITY MATERIAL

REF: NDA 88-482
Amendment to Abbreviated, Unapproved Application
Dissolution Studies
Product: Disulfiram Tablets, USP 250mg.

Dear Dr. Seife:

We refer to our Abbreviated New Drug Application, NDA 88-482, dated August 22, 1983, for the pharmaceutical dosage form Disulfiram Tablets, USP 250mg.

Reference is made to your letter dated October 13, 1983, wherein you cite that the application is deficient in that it fails to perform adequate dissolution studies.

Therefore, we hereby submit in triplicate comparative dissolution profiles pursuant to your request and in order to remove the deficiencies as noted.

We trust this information will meet with your approval and thank you for your kind and prompt attention to this matter.

Sincerely yours,

Satish P. Patel, Ph.D.
President

SIDMAK LABORATORIES, INC.

NOV - 1 1983

SPP:lk
encs.

NDA 88-482

OCT 24 1983

Sidmak Laboratories, Inc.
Attention: Satish Patel, Ph.D.
17 West Street, P.O. Box 371
East Hanover, New Jersey 07936

Gentlemen:

Please refer to your abbreviated new drug application dated August 22, 1983, submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for Disulfiram Tablets, 250 mg.

The application is deficient and therefore not approvable under Section 505(b) of the Act as follows:

1. It fails to include a satisfactory package insert. In this regard:

   a) How supplied: Note scored or unscored for each strength.
   b) Also: Issued, month/year.

2. It fails to include an appropriate Drug Master File referral from

3. It fails to submit adequate information with respect to the test methods employed for the container, closure, or other component parts of the drug package upon receiving to assure their suitability for the intended use.

4. It fails to include an outline of manufacturing procedures for this specific drug expanded to include the operation procedures and precautions necessitated by the light sensitivity of active ingredient and dosage form.

5. It fails to submit the adequate stability information. In this regard:

   a) Cite/describe methodology (stability indicating assay) and test conditions: procedures for detecting the presence of degradation product(s).

   b) Include the proposed schedule of testing at controlled room temperature. It is recommended that the studies be performed at initial, 3, 6, 12, 18, and 24 months and yearly thereafter in the container/closure system in which the drug is to be marketed at controlled room temperature.

c) Two year expiration dating: We are unable to reach any conclusion based on the limited data submitted. It is recommended that data be obtained for production lots at challenge conditions for three months to justify the proposed expiration dating prior to approval.

d) Samples Placed on Stability:

1) The first three production lots of the product should be placed on stability. In the case where more than one package size is marketed, the first 3 production lots of the smallest and the largest size (e.g., 3 lots of 100 tablet bottles and 3 lots of 500 tablet bottles) should be placed on stability. Also, if more than one container/ closure system is used for a particular size, stability data in each container/ closure system is necessary.

2) Yearly thereafter, 1 production batch should be added to the stability program.

6. It fails to respond to our letter of October 13, 1983.

The file is now closed. If you wish to reopen it, the submission should be in the form of an amendment to this application, adequately organized, which represents the information necessary to remove all deficiencies we have outlined.

If you do not agree with our conclusions, you may make a written request to file the application over protest, as authorized by 21 CFR 314.110(d). If you do so, the application shall be re-evaluated and within 90 days of the date of receipt of such request (or additional period as we may agree upon), the application shall be approved or you shall be given a written notice of opportunity for a hearing on the question of whether the application is approvable.

Sincerely yours,

10/24/83

Marvin Seife, M.D.
Director
Division of Generic Drugs
Office of Drug Standards
National Center for Drugs and Biologics

cc: NWK-DO
HFN-530
JMeyer/CChan
R/D INITIAL JMeyer/MSeife
mmorgan: 10/21/83 (2076c)
Not approvable

10/21/83
10-21-83

REVIEW OF PROFESSIONAL LABELING

ANDA - DRAFT

DATE OF REVIEW: 10-17-83

NAME OF FIRM: Sidmak Labs., Inc.

ANDA #: 88-482 (250 mg)
88-483 (500 mg)

NAME OF DRUG: Generic: Disulfiram

DATE OF SUBMISSION: 8-22-83

COMMENTS:

Container: satisfactory

100s, 500s (500 mg)

100s, 1000s (250 mg)

Insert: Not satisfactory.

a) HOW SUPPLIED: Note scored or unscored for each strength

b) Also: Issued, Month/Year

RECOMMENDATIONS:

1. Inform firm of the above comments.
2. Request FPL container labels.
3. Request they make minor revisions on insert labeling, then prepare and submit FPL.

Kent T. Johnson

cc:
dup
KTJ/cl/10-17-83

ABBREVIATED NEW-DRUG APPLICATION OR SUPPLEMENT

Statement Date: DES: 7888

NDA # 88-482

NAME AND ADDRESS OF APPLICANT:

Sidmak Laboratories, Inc.
East Hanover, NJ 07936

ORIGINAL X
AMENDMENT
SUPPLEMENT
RESUBMISSION
CORRESPONDENCE
REPORT
OTHER

PURPOSE OF AMENDMENT/SUPPLEMENT

DATE(s) of SUBMISSION(s)

As per letter

PHARMACOLOGICAL CATEGORY	NAME OF DRUG
Alcohol deterrent Antabuse	Disulfiram
DOSAGE FORM	POTENCY(IES)
Tablets	250 mg.
STERILIZATION	SAMPLES
NA	NA (USP)

HOW DISPENSED
Rx X OTC

RELATED IND/NDA/DMF

88-483 500 mg
88-482 250 mg

LABELING

Unsatisfactory per K. Johnson

BIOLOGIC AVAILABILITY

Need dissolution per Dr. Dighe on 9-6-83

ESTABLISHMENT INSPECTION

Requested

COMPONENTS, COMPOSITION, MANUFACTURING, CONTROLS

See issued letter

PACKAGING

White opaque H.D. polyethylene bottles and metal cap, inner form seal

STABILITY:

Protocol: See issued letter

Exp. Date: Firm request for 2 yrs.

REMARKS & CONCLUSION:

Not approvable

OCT 13 1983

NDA 83-482

Sidmak Laboratories, Inc.
Attention: Satish Patel, Ph.D.
17 West Street, P.O. Box 371
East Hanover, NJ 07936

Gentlemen:

Please refer to your new drug application dated August 22, 1983 submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for Disulfiram Tablets, 250 mg.

The application is deficient and therefore not approvable under Section 505(b) of the Act as follows:

(1) It fails to perform the adequate dissolution studies. In this regard:

Our Division of Biopharmaceutics is developing dissolution specifications and tests for disulfiram dosage forms. In accord with this development we are requesting comparative dissolution profiles for a minimum of 12 individual tablets - dosage firm vs. the appropriate reference product as per the following conditions:

a. 900 ml water, 37°C, paddle, 50 rpm at 15, 30, 45 and 60 minute intervals.

b. 900 ml 0.1 N HCl, 37°C, paddle, 50 rpm at 15, 30, 45 and 60 minute inverals.

c. 900 ml simulated intestinal fluid without enzyme, paddle, 50 rpm at 15, 30, 45 and 60 minute intervals.

(2) We will correspond with you further after we have had the opportunity to review the labeling and other parts of this application.

The file is now closed. If you wish to reopen it, the submission should be in the form of an amendment to this application, adequately organized, which represents the information necessary to remove all deficiencies we have outlined.

If you do not agree with our conclusions, you may make a written request to file the application over protest, as authorized by 21 CFR 314.110(d). If you do so, the application shall be re-evaluated and within 90 days of the date of receipt of such request (or additional period as we may agree upon), the application shall be approved or you shall be given a written notice of opportunity for a hearing on the question of whether the application is approvable.

Sincerely yours,

Marvin Seife 10/13/83

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of the Associate Director for
Drug Monographs
Office of Drugs
National Center for Drugs & Biologics

cc:
NWK-DO
HFN-530
JLMeyer/CChan 10-12-83
R/DinitJMeyer/MSeife
ft/cjl/10-12-83
not approvable
id 10/83

NOV 8 1983

Disulfuram
250 mg Tablets
ANDA # 88-482
Reviewer: L.A. Ouderkirk
Wang # 2686e

Sidmak Laboratories, Inc.
East Hanover, New Jersey
Submission Date:
August 22, 1983

Review of a Submission

This submission contains only disintegration testing data for the firm's 250 mg disulfiram tablets. No dissolution testing data was submitted.

The firm has subsequently submitted dissolution testing data for this product in their submission dated October 25, 1983.

Recommendation:

1. The Division of Biopharmaceutics need not to review this submission, because the firm has submitted additional dissolution data.

2. The Division of Biopharmaceutics will review the dissolution data included in the firm's October 25, 1983 submission.

11-7-83
Larry A. Ouderkirk, Biologist
Biopharmaceutics Review Branch

Initialed by C.M.Ise

cc: ANDA # 88-482 orig., HFN-530 (4), HFN-522 (Ouderkirk, Ise - 2), HFN-503 (Hare), Chron File, Drug File, Review File, Division File

LAO/dea/Wang # 2686e

AUG 26 1983

NDA 88-482

Sidmak Laboratories, Inc.
Attention: Satish Patel, Ph.D.
17 West Street, P.O. Box 371
East Hanover, NJ 07936

Gentlemen:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

NAME OF DRUG: Disulfiram Tablets, 250 mg.

DATE OF APPLICATION: August 22, 1983

DATE OF RECEIPT: August 24, 1983

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the NDA number shown above.

Sincerely yours,

for 8-26-83

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Office of the Associate Director
for Drug Monographs
Office of Drugs
National Center for Drugs and Biologics

NWK-DO DUP HFN-530
JLMeyer/mlb/8-25-83
ack

8/20/83

ANDA ADMINISTRATIVE CONTROL RECORD

Applicant Sidmak Laboratories P No._____

ANDA # 88-482

Trade Name Disulfiram RX ✓ OTC___ Date Recd. 8-24-83

Generic Name/Dosage Form/Strength: Disulfiram Tablets 250mg

DESI Drug ✓ DESI No._____ DESI Date(FR)_____

Similar or Related_____ Name of DESI Drug_____

Applicant Manufactuer: Yes ✓ No_____.

If No: Name of Manufacturer _____

ANDA #_____ (Approved:_____ Pending_____ Same Formulation___

Application Complete (See Pg. 2): YES ✓ NO_____
Application Acceptable: YES ✓ NO_____
REMARKS:

Letter to Firm: Acknowledgement 22631 Not-acceptable_____ Date_____

DLR

CSO: M Bennett Date 8/25/83

BIO Review Required: Yes X NO___ In Vitro X In Vivo_____
Date Fwd:_____

Medical Officer SEIFE Reveiw Completed_____ R.R____

Chemist Chang Reveiw Completed_____ R.R.____

Inspection Request to HFD 320(date): 8/25/83 Reply Rec.(date)_____

Letter to Firm: Labeling Review (date)_____ Response(date)_____

Chemistry: 1)(date) _____ Response_____
2)(date) _____ Response_____

Approvable Date_____

Withdrawal Date_____

Special Instructions/Action- 8/2,/83

3566A/HTB

CSO_____ Date____

88-482

11. Completeness of Submission

	Yes	No
Cover Letter	✓	
356h Signed	✓	
Table of Contents	✓	
Labeling	✓ draft	
Statement re Rx/OTC Status	✓	
Components & Composition (Unit Composition)	✓	
Manufacturing Controls	✓	
Batch Formulation		
Certification of GMP	✓	
Description of Facilities		
Manufacturing Processes (Batch Records)	✓	
Specs & Tests for Active Ingredient and Finished Dosage Form	✓	
Stability Profile Including Stability Data (Use of Stability indicating method)	✓	
Samples Statement Plus Data		
Bio Protocol (If Applicable)	—	
Dissolution Data (If Applicable)		
Environmental Impact Analysis	✓	

Bio Data protocol_____

Study: IN VIVO_____ IN VITRO_____

Reviewed Date_____ Approved_____

Deficiency Letter Sent, Date_____

JCMorrison/mlb/6-10-80
5218P

DEPARTMENT OF HEALTH & HUMAN SERVICES

Memorandum

TO :Manufacturing Review Branch (HFN-322) DATE: 8-25-83
Division of Drug Quality Compliance

FROM :Division of Generic Drugs
Requester's Name David Rosen PHONE: 443-4080

SUBJECT: ESTABLISHMENT EVALUATION REQUEST

NDA, ANDA, AND SUPPLEMENT NUMBER: 88-482 (250 mg) 88-483 (500 mg)

DRUG TRADE MARK (if any) _____

DRUG NONPROPRIETARY NAME: Disulfiram [illegible] Tablets, 250 mg. 500 mg.

DOSAGE FORM AND STRENGTH(S): TCM

DRUG CLASSIFICATION: PROFILE CLASS CODE:
(Priority) _____ A or B _____ 1C _____ Other _____ _____

APPLICANT'S NAME: Sidmak Laboratories, Inc.
ADDRESS: 17 West Street, P.O. Box 371, East Hanover, NJ 07936

FACILITIES TO BE EVALUATED: (Name, Full Address, DMF# (if any), and Responsibility)

1. applicant

Comments: ( ) See Attached.
( ) Actual on-site inspection requested.

Reason: _____

****

FOR HFN-322 USE ONLY:

Request Rec'd: _____ Inspection Requested: _____
(if applicable)

Firm(s) are in Compliance With GMPs: _____
Basis for Decision: _____
Reviewing CSO: _____ Concurrance: _____

cc: HFN-____
HFN-____
HFN-322

FORM FDA 3274 (1/83)

cc: Harrow Rm. 12-87 HFD-503

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service

O : Dr. Marvin Seife
Director, Division of Generic Drug Products (HFD-530)
THROUGH: Director, Division of Biopharmaceutics (HFD-520)
Chief, Biopharmaceutics Review Branch
Division of Biopharmaceutics (HFD-522)

DATE: February 20, 1981

2/26/81

ROM : Group Leader, ANDA Review,
Biopharmaceutics Review Branch, Division of Biopharmaceutics (HFD-522)

UBJECT: Disulfiram Bioavailability

The Division of Biopharmaceutics has determined that in vivo bioavailability studies are not required for disulfiram tablets (Antabuse, Ayerst). Dissolution testing data for this drug product was requested of Danbury Laboratories as a basis of approval.

The firm conducted dissolution testing of the test and Ayerst drug products in water, simulated gastric fluid, and simulated intestinal fluid, and found very little of the active ingredient was soluble in aqueous media. The Division of Biopharmaceutics asked the firm to develop a dissolution profile for disulfiram over a pH range of 1.2 - 9.0 and also in 10% ethanol in water mixture. It was found that less than 10% of the pure disulfiram was soluble in 900 ml of any of the media. Further, studies by the firm demonstrated that the solubility of disulfiram in water containing 0.05 and 0.1 per cent Tween 80 (surfactant) was 20.6 and 29.5 per cent respectively.

The Division of Biopharmaceutics recommends that dissolution testing for Disulfiram Tablets, 250 and 500 mg tablets be deferred. The firms intending to market the drug product should, however, be informed that when appropriate dissolution methodology becomes available they will be required to conduct dissolution testing.

Charles M. Ise, Ph.D.

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

TO : Charles Y. Chang
Chemist, HFD-530

DATE: July 23, 1979

THROUGH: Director, Division of Biopharmaceutics, HFD-520

FROM : Acting Chief,
Biopharmaceutics Review Branch, HFD-522

SUBJECT: Bioavailability Requirement for Disulfiram (Antabuse)

1. DESI notice on Disulfiram states that an acceptable bioavailability study should be conducted by an applicant as a condition for approval of abbreviated new drug application. You have requested the Division of Biopharmaceutics to make a determination whether this requirement should be waived.

2. Disulfiram arrests the oxidation of ingested alcohol at acetaldehyde stage. The accumulation of acetaldehyde causes flushing, pounding of the heart and head, dyspnea and nausea. The reaction may be fatal. Distressing side effects of disulfiram are nausea, vomiting, impaired taste, bad breath, drowsiness and impotence. In view of the severity of action and toxic side effects, the Division of Biopharmaceutics recommends that the bioavailability requirement for Disulfiram be waived as a condition for approval of ANDA.

3. In order to assure adequate performance biologically the Division of Biopharmaceutics recommends that dissolution testing be conducted on Disulfiram tablets. Comparative dissolution testing should be conducted under the following conditions using Ayerst Antabuse tablets as the reference product:

a. 900 ml of simulated gastric fluid at 37°C; USP method II (paddle); paddle rotation speed 50 rpm.

b. 900 ml of simulated intestinal fluid at 37°C; USP Method II (paddle); paddle rotation speed 50 rpm.

Shrikant V. Dighe, Ph.D.

Sidmak
LABORATORIES, INC.

17 WEST STREET • P.O. BOX 371 • EAST HANOVER, NJ 07936 • TELEPHONE: (201) 386-5566

August 22, 1983

Marvin Seife, M.D., Director
Division of Generic Drug Monographs
Office of the Associate Director for Drug Monographs
Office of Drugs
National Center for Drugs and Biologics
5600 Fishers Lane
Rockville, Maryland 20852

ABBREVIATED
NEW DRUG APPLICATION

Re: Abbreviated New Drug Application
Product: Disulfiram Tablets, USP 250mg

DRAFT LABELING

Dear Dr. Seife:

Pursuant to section 505(b) of the Federal Food, Drug and Cosmetic Act, we are submitting herewith, in triplicate, an Abbreviated New Drug Application for the product mentioned above.

Included in this submission are:

1. Form 356-H
2. Volume No. 1 Copy No. 1 (Blue Folder)
3. Volume No. 1 Copy No. 2 (Red Folder)
4. Volume No. 1 Copy No. 3 (Yellow Folder)

Respectfully Submitted,

SIDMAK LABORATORIES, INC.

Satish Patel, Ph.D.
President

RECEIVED
AUG 24 1983

GENERIC DRUGS