CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

40-349

Generic Name: Sulfasalazine Tablets USP, 500mg

Sponsor: Vintage Pharmaceuticals, Inc.

Approval Date: January 11, 2002

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-349

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CENTER FOR DRUG EVALUATION AND RESEARCH

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APPROVAL LETTER

ANDA 40-349

JAN 11 2002

Vintage Pharmaceuticals, Inc.
Attention: Christopher J. Nascone
3241 Woodpark Blvd.
Charlotte, NC 28206

Dear Sir:

This is in reference to your abbreviated new drug application dated November 30, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Sulfasalazine Tablets USP, 500 mg.

Reference is also made to your amendment dated December 13, 2001.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Sulfasalazine Tablets USP, 500 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Azulfidine Tablets, 500 mg, of Pharmacia and UpJohn Co.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy that you intend to use in your initial 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 Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

Robert Lumpkin for 1/11/2002

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-349

FINAL PRINTED LABELING

SULFASALAZINE TABLETS, USP

Rx only

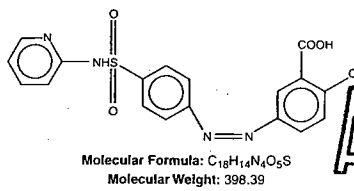
JAN 11 2002

DESCRIPTION:
Sulfasalazine tablets, USP 500 mg for oral administration.

Therapeutic classification: Anti-inflammatory agent.

Chemical designation: 5-([p-(2-Pyridylsulfamoyl)phenyl]azo) salicylic acid.

Structural Formula:



Molecular Formula: $C_{18}H_{14}N_4O_5S$
Molecular Weight: 398.39

APPROVED

Inactive Ingredients: cornstarch, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, partially pregelatinized starch, polyvinyl pyrilidone, purified water, and talc.

CLINICAL PHARMACOLOGY:

Pharmacodynamics

The mode of action of sulfasalazine (SSZ) or its metabolites, 5-aminosalicylic acid (5-ASA) and sulfapyridine (SP), is still under investigation, but may be related to the anti-inflammatory and/or immunomodulatory properties that have been observed in animal and in vitro models, to its affinity for connective tissue, and/or to the relatively high concentration it reaches in serous fluids, the liver and intestinal walls, as demonstrated in autoradiographic studies in animals. In ulcerative colitis, clinical studies utilizing rectal administration of SSZ, SP, and 5-ASA have indicated that the major therapeutic action may reside in the 5-ASA moiety.

Pharmacokinetics

In vivo studies have indicated that the absolute bioavailability of orally administered SSZ is less than 15% for parent drug. In the intestine, SSZ is metabolized by intestinal bacteria to SP and 5-ASA. Of the two species, SP is relatively well absorbed from the intestine and highly metabolized, while 5-ASA is much less well absorbed.

Absorption: Following oral administration of 1 g of SSZ to 9 healthy males, less than 15% of a dose of SSZ is absorbed as parent drug. Detectable serum concentrations of SSZ have been found in healthy subjects within 90 minutes after the ingestion. Maximum concentrations of SSZ occur between 3 and 12 hours post-ingestion, with the mean peak concentration (6 µg/mL) occurring at 6 hours.

In comparison, peak plasma levels of both SP and 5-ASA occur approximately 10 hours after dosing. This longer time to peak is indicative of gastrointestinal transit to the lower intestine where bacteria mediated metabolism occurs. SP apparently is well absorbed from the colon with an estimated bioavailability of 60%. In this same study, 5-ASA is much less well absorbed from the gastrointestinal tract with an estimated bioavailability of from 10 to 30%.

Distribution: Following intravenous injection, the calculated volume of distribution (Vdss) for SSZ was 7.5 ± 1.6 L. SSZ is highly bound to albumin (>99.3%) while SP is only about 70% bound to albumin. Acetylsulfapyridine (AcSP), the principal metabolite of SP, is approximately 90% bound to plasma proteins.

Metabolism: As mentioned above, SSZ is metabolized by intestinal bacteria to SP and 5-ASA. Approximately 15% of a dose of SSZ is absorbed as parent and is metabolized to some extent in the liver to the same two species. The observed plasma half-life for intravenous sulfasalazine is 7.6 ± 3.4 hours. The primary route of metabolism of SP is via acetylation to form AcSP. The rate of metabolism of SP to AcSP is dependent upon acetylator phenotype. In fast acetylators, the mean plasma half-life of SP is 10.4 hours while in slow acetylators, it is 14.8 hours. SP can also be metabolized to 5-hydroxy-sulfapyridine (SPOH) and N-acetyl-5-hydroxy-sulfapyridine. 5-ASA is primarily metabolized in both the liver and intestine to N-acetyl-5-aminosalicylic acid via a non-acetylation phenotype dependent route. Due to low plasma levels produced by 5-ASA after oral administration, reliable estimates of plasma half-life are not possible.

Excretion: Absorbed SP and 5-ASA and their metabolites are primarily eliminated in the urine either as free metabolites or as glucuronide conjugates. The majority of 5-ASA stays within the colonic lumen and is excreted as 5-ASA and acetyl-5-ASA with the feces. The calculated clearance of SSZ following intravenous administration was 1 L/hr. Renal clearance was estimated to account for 37% of total clearance.

Special Populations

Elderly: Elderly patients with rheumatoid arthritis showed a prolonged plasma half-life for SSZ, SP, and their metabolites. The clinical impact of this is unknown.

Acetylator Status: The metabolism of SP to AcSP is mediated by polymorphic enzymes such that two distinct populations of slow and fast metabolizers exist. Approximately 60% of the Caucasian population can be classified as belonging to the slow acetylator phenotype. These subjects will display a prolonged plasma half-life for SP (14.8 hours vs 10.4 hours) and an accumulation of higher plasma levels of SP than fast acetylators. The clinical implication of this is unclear; however, in a small pharmacokinetic trial where acetylator status was determined, subjects who were slow acetylators of SP showed a higher incidence of adverse events.

Gender: Gender appears not to have an effect on either the rate or the pattern of metabolites of SSZ, SP, or 5-ASA.

INDICATIONS AND USAGE:

Sulfasalazine is indicated:

a. in the treatment of mild to moderate ulcerative colitis, and as adjunctive therapy in severe ulcerative colitis.

b. for the prolongation of the remission period between acute attacks of ulcerative colitis.

CONTRAINDICATIONS:

Sulfasalazine Tablets are contraindicated in:

Pediatric patients under two years of age,
Patients with intestinal or urinary obstruction,
Patients with porphyria,
Patients hypersensitive to sulfasalazine, its metabolites, sulfonamides, or salicylates.

WARNINGS:

Only after critical appraisal should sulfasalazine be given to patients with hepatic or renal damage or blood dyscrasias. Deaths associated with the administration of sulfasalazine have been reported from hypersensitivity reactions, agranulocytosis, aplastic anemia, other blood dyscrasias, renal and liver damage, irreversible neuromuscular and central nervous system changes, and fibrosing alveolitis. The presence of clinical signs such as sore throat, fever, pallor, purpura or jaundice may be indications of serious blood disorders. Complete blood counts, as well as an urinalysis with careful microscopic examination, should be done frequently in patients receiving sulfasalazine (see Laboratory Tests). Oligospermia and infertility have been observed in men treated with sulfasalazine. Withdrawal of the drug appears to reverse these effects.

PRECAUTIONS:

General: Sulfasalazine should be given with caution to patients with severe allergy or bronchial asthma. Adequate fluid intake must be maintained in order to prevent crystalluria and stone formation. Patients with glucose-6-phosphate dehydrogenase deficiency should be observed closely for signs of hemolytic anemia. This reaction is frequently dose related. If toxic or hypersensitivity reactions occur, the drug should be discontinued immediately.

Information for Patients: Patients should be informed of the possibility of adverse reactions and of the need for careful medical supervision. The occurrence of sore throat, fever, pallor, purpura, or jaundice may indicate a serious blood disorder. Should any of these occur, the patient should seek medical advice. They should also be made aware that ulcerative colitis rarely remits completely, and that the risk of relapse can be substantially reduced by continued administration of sulfasalazine at a maintenance dosage. Patients should be instructed to take sulfasalazine in evenly divided doses preferably after meals. Additionally, patients should be advised that sulfasalazine may produce an orange-yellow discoloration of the urine or skin.

Laboratory Tests: Complete blood counts, including differential white cell count and liver function tests, should be performed before starting sulfasalazine and every second week during the first three months of therapy. During the second three months, the same tests should be done once monthly and thereafter once every three months, and as clinically indicted. Urinalysis and an assessment of renal function should also be done periodically during treatment with sulfasalazine.

The determination of serum sulfapyridine levels may be useful since concentrations greater than 50 µg/mL appear to be associated with an increased incidence of adverse reactions.

Drug Interactions: Reduced absorption of folic acid and digoxin have been reported when those agents were administered concomitantly with sulfasalazine.

Drug/Laboratory Test Interactions: The presence of sulfasalazine or its metabolites in body fluids has not been reported to interfere with laboratory test procedures.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two-year oral carcinogenicity studies were conducted in male and female F344/N rats and B6C3F1 mice. Sulfasalazine was tested at 84 (496 mg/m²), 168 (991 mg/m²), and 337.5 (1991 mg/m²) mg/kg/day doses in rats. A statistically significant increase in the incidence of urinary bladder transitional cell papillomas was observed in the male rats. In female rats, two (4%) of the 337.5 mg/kg rats had transitional cell papilloma of the kidney. The increased incidence of neoplasms in the urinary bladder and kidney of rats was also associated with an increase in the renal calculi formation and hyperplasia of transitional cell epithelium. For the mouse study, sulfasalazine was tested at 675 (2025 mg/m²), 1350 (4050 mg/m²), and 2700 (8100 mg/m²) mg/kg/day. The incidence of hepatocellular adenoma or carcinoma in male and female mice was significantly greater than the control at all doses tested.

Sulfasalazine did not show mutagenicity in the bacterial reverse mutation assay (Ames test) and in L51784 mouse lymphoma cell assay at the HGPRT gene. However, sulfasalazine showed equivocal mutagenic response in the micronucleus assay of mouse and rat bone marrow and mouse peripheral RBC and in the sister chromatid exchange, chromosomal aberration, and micronucleus assays in lymphocytes obtained from humans.

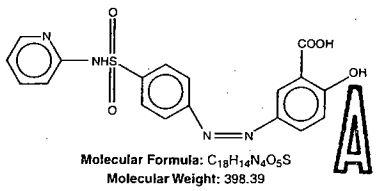
Impairment of male fertility was observed in reproductive studies performed in rats at a dose of 800 mg/kg/day (4800 mg/m²). Oligospermia and infertility have been described in men treated with sulfasalazine. Withdrawal of the drug appears to reverse these effects.

Pregnancy:

Teratogenic Effects:

Pregnancy Category B: Reproduction studies have been performed in rats and rabbits at doses up to 6 times the human dose and have revealed no evidence of impaired female fertility or harm to the fetus due to sulfasalazine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

A national survey evaluated the outcome of pregnancies associated with inflammatory bowel disease (IBD). In a group of 186 women treated with sulfasalazine alone or sulfasalazine and concomitant steroid therapy, the incidence of fetal morbidity and mortality was comparable to that for 245 untreated IBD pregnancies as well as pregnancies in the general population.[1] A study of 1,455 pregnancies associated with exposure to sulfon-



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A national survey evaluated the outcome of pregnancies associated with inflammatory bowel disease (IBD). In a group of 186 women treated with sulfasalazine alone or sulfasalazine and concomitant steroid therapy, the incidence of fetal morbidity and mortality was comparable to that for 245 untreated IBD pregnancies as well as pregnancies in the general population.[1] A study of 1,455 pregnancies associated with exposure to sulfonamides indicated that this group of drugs, including sulfasalazine, did not appear to be associated with fetal malformation.[2] A review of the medical literature covering 1,155 pregnancies in women with ulcerative colitis suggested that the outcome was similar to that expected in the general population.[3]

No clinical studies have been performed to evaluate the effect of sulfasalazine on the growth development and functional maturation of children whose mothers received the drug during pregnancy.

Nonteratogenic Effects: Sulfasalazine and sulfapyridine pass the placental barrier. Although sulfapyridine has been shown to have a poor bilirubin-displacing capacity, the potential for kernicterus in newborns should be kept in mind.

A case of agranulocytosis has been reported in an infant whose mother was taking both sulfasalazine and prednisone throughout pregnancy.

Nursing Mothers: Caution should be exercised when sulfasalazine is administered to a nursing woman. Sulfonamides are excreted in the milk. In the newborn, they compete with bilirubin for binding sites on the plasma proteins and may thus cause kernicterus. Insignificant amounts of uncleaved sulfasalazine have been found in milk, whereas the sulfapyridine levels in milk are about 30 to 60 percent of those in the maternal serum. Sulfapyridine has been shown to have a poor bilirubin-displacing capacity.

Pediatric Use: Safety and effectiveness in pediatric patients below the age of two years have not been established.

ADVERSE REACTIONS:
The most common adverse reactions associated with sulfasalazine are anorexia, headache, nausea, vomiting, gastric distress and apparently reversible oligospermia. These occur in about one-third of the patients. Less frequent adverse reactions are skin rash, pruritus, urticaria, fever, Heinz body anemia, hemolytic anemia and cyanosis which may occur at a frequency of one in every thirty patients or less. Experience suggests that with a daily dosage of 4 g or more, or total serum sulfapyridine levels above 50 mcg/mL, the incidence of adverse reactions tends to increase.

Although the listing which follows includes a few adverse reactions which have not been reported with this specific drug, the pharmacological similarities among the sulfonamides require that each of these reactions be considered when sulfasalazine is administered. Other adverse reactions which occur rarely, in approximately 1 in 1000 patients or less are as follows:

Blood dyscrasias: aplastic anemia, agranulocytosis, leukopenia, megaloblastic (macrocytic) anemia, purpura, thrombocytopenia, hypoprothrombinemia, methemoglobinemia, congenital neutropenia, and myelodysplastic syndrome.

Hypersensitivity reactions: erythema multiforme (Stevens-Johnson syndrome), exfoliative dermatitis, epidermal necrolysis (Lyell's syndrome) with corneal damage, anaphylaxis, serum sickness syndrome, pneumonitis with or without eosinophilia, vasculitis, fibrosing alveolitis, pleuritis, pericarditis with or without tamponade, allergic myocarditis, polyarteritis nodosa, lupus erythematosus-like syndrome, hepatitis and hepatic necrosis with or without immune complexes, fulminant hepatitis, sometimes leading to liver transplantation, parapsoriasis varioliformis acuta (Mucha-Haberman syndrome), rhabdomyolysis, photosensitization, arthralgia, periorbital edema, conjunctival and scleral injection, and alopecia.

Gastrointestinal reactions: hepatitis, pancreatitis, bloody diarrhea, impaired folic acid absorption, impaired digoxin absorption, stomatitis, diarrhea, abdominal pains, and neutropenic enterocolitis.

Central nervous system reactions: transverse myelitis, convulsions, meningitis, transient lesions of the posterior spinal column, cauda equina syndrome, Guillain-Barre syndrome, peripheral neuropathy, mental depression, vertigo, hearing loss, insomnia, ataxia, hallucinations, tinnitus, and drowsiness.

Renal reactions: toxic nephrosis with oliguria and anuria, nephritis, nephrotic syndrome, hematuria, crystalluria, proteinuria, and hemolytic-uremic syndrome.

Other reactions: urine discoloration and skin discoloration.

The sulfonamides bear certain chemical similarities to some goitrogens, diuretics (acetazolamide and the thiazides), and oral hypoglycemic agents. Goiter production, diuresis and hypoglycemia have occurred rarely in patients receiving sulfonamides. Cross-sensitivity may exist with these agents. Rats appear to be especially susceptible to the goitrogenic effects of sulfonamides and long-term administration has produced thyroid malignancies in this species.

Postmarketing Reports
The following events have been identified during post-approval use of products which contain (or are metabolized to) mesalamine in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of seriousness, frequency of reporting, or potential causal connection to mesalamine:

Gastrointestinal: Reports of hepatotoxicity, including elevated liver function tests (SGOT/AST, SGPT/ALT, GGT, LDH, alkaline phosphatase, bilirubin), jaundice, cholestatic jaundice, cirrhosis, and possible hepatocellular damage including liver necrosis and liver failure. Some of these cases were fatal. One case of Kawasaki-like syndrome, which included hepatic function changes, was also reported.

DRUG ABUSE AND DEPENDENCE:
None Reported

OVERDOSAGE:
There is evidence that the incidence and severity of toxicity following overdosage are directly related to the total serum sulfapyridine concentration. Symptoms of overdosage may include nausea, vomiting, gastric distress, and abdominal pains. In more advanced cases, CNS symptoms such as drowsiness, convulsions, etc. may be observed. Serum sulfapyridine concentrations may be used to monitor the progress of recovery from overdosage.

There are no documented reports of deaths due to ingestion of large single doses of sulfasalazine.

It has not been possible to determine the oral LD_{50} in laboratory animals such as mice, since the highest daily oral dose which can be given (12 g/kg) is not lethal. Doses of sulfasalazine of 16 g per day have been given to patients without mortality.

Instructions for overdosage: Gastric lavage or emesis plus catharsis as indicated. Alkalinize urine. If kidney function is normal, force fluids. If anuria is present, restrict fluids and salt, and treat appropriately. Catheterization of the ureters may be indicated for complete renal blockage by crystals. The low molecular weight of sulfasalazine and its metabolites may facilitate their removal be dialysis. For agranulocytosis, discontinue the drug immediately, hospitalize the patient and institute appropriate therapy. For hypersensitivity reactions, discontinue treatment immediately. Such reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. When in the physician's opinion, reinstitution of sulfasalazine is warranted, regimens modeled upon desensitization procedures may be attempted approximately two weeks after sulfasalazine has been discontinued and symptoms have disappeared (see **"DOSAGE AND ADMINISTRATION"**).

DOSAGE AND ADMINISTRATION:
Dosage of sulfasalazine tablets should be adjusted to each individual's response and tolerance. The drug should be given in evenly divided doses over each 24-hour period; intervals between nighttime doses should not exceed 8 hours, with administration after meals recommended when feasible. Experience suggests that with daily dosages of 4 g or more, the incidence of adverse reactions tends to increase; hence, patients receiving these dosages should be instructed about, and carefully observed for, the appearance of adverse effects.

Some patients may be sensitive to treatment with sulfasalazine. Various desensitization-like regimens have been reported to be effective in 34 of 53 patients,[4] 7 of 8 patients,[5] and 19 of 20 patients.[6] These regimens suggest starting with a total daily dose of 50 to 250 mg sulfasalazine initially and doubling it every 4 to 7 days until the desired therapeutic level is achieved. If the symptoms of sensitivity recur, sulfasalazine should be discontinued. Desensitization should not be attempted in patients who have a history of agranulocytosis or who have experienced an anaphylactoid reaction while previously receiving sulfasalazine.

USUAL DOSAGE:
Initial Therapy:
Adults: 3 to 4 g daily in evenly divided doses. In some cases, it is advisable to initiate therapy with a smaller dosage, e.g. 1 to 2 g daily, to reduce possible gastrointestinal intolerance. If daily doses exceeding 4 g are required to achieve desired effects, the increased risk of toxicity should be kept in mind.

Children, two years of age and older: 40 to 60 mg/kg body weight in each 24-hour period, divided into 3 to 6 doses.

Maintenance Therapy:
Adults: 2 g daily.

Children, two years of age and older: 30 mg/kg body weight in each 24-hour period, divided into 4 doses.

The response of acute ulcerative colitis to sulfasalazine tablets can be evaluated by clinical criteria, including the presence of fever, weight changes, and degree and frequency of diarrhea and bleeding, as well as by sigmoidoscopy and the evaluation of biopsy samples. It is often necessary to continue medication even when clinical symptoms, including diarrhea, have been controlled. When endoscopic examination confirms satisfactory improvement, the dosage of sulfasalazine is reduced to a maintenance level. If diarrhea recurs, the dosage should be increased to previously effective levels. If symptoms of gastric intolerance (anorexia, nausea, vomiting, etc.) occur after the first few doses of sulfasalazine, they are probably due to increased serum levels of total sulfapyridine and may be alleviated by halving the daily dose of sulfasalazine and subsequently increasing it gradually over several days. If gastric intolerance continues, the drug should be stopped for 5 to 7 days, then reintroduced at a lower daily dose.

HOW SUPPLIED:
Sulfasalazine tablets, USP, 500 mg are round, gold-colored, scored tablets, debossed "5904" and "V" on one side and plain on the other in the following package sizes: 100, 500, 1000.

Storage:
Store between 15° to 30°C (59° to 86°F), see USP.

REFERENCES:

1. Mogadam M, et al. Pregnancy in inflammatory bowel disease: effect of sulfasalazine and corticosteroids on fetal outcome. Gastroenterology 1981;80:72-6.
2. Kaufman DW, editor. Birth defects and drugs during pregnancy. Littleton, MA: Publishing Sciences Group, Inc. 1977:296-313.
3. Jarnerot G. Fertility, sterility and pregnancy in chronic inflammatory bowel disease. Scand J Gastroenterol 1982;17:1-4.
4. Korelitz B, et al. Desensitization to sulfasalazine in allergic patients with IBD: an important therapeutic modality. Gastroenterology 1982;82:1104.
5. Holdworth CG. Sulphasalazine desensitization. Br Med J 1981;282:110.
6. Taffet SL, Das KM. Desensitization of patients with inflammatory bowel disease to sulfasalazine. Am J Med 1982;73:520-4.

Rx only

Manufactured by:
VINTAGE PHARMACEUTICALS, INC.
Charlotte, NC 28206

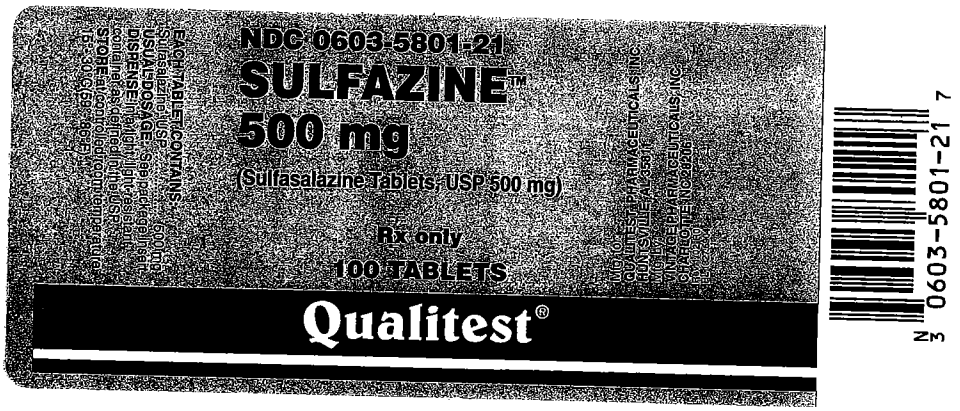
IN-165
Rev 8/00
R4

Sulfasalazine Tablets
500 mg
Annual Report

Product Labeling

Sulfasalazine Tablets
500 mg
ANDA #40-349

100-Count NDC# 0603-5801-21

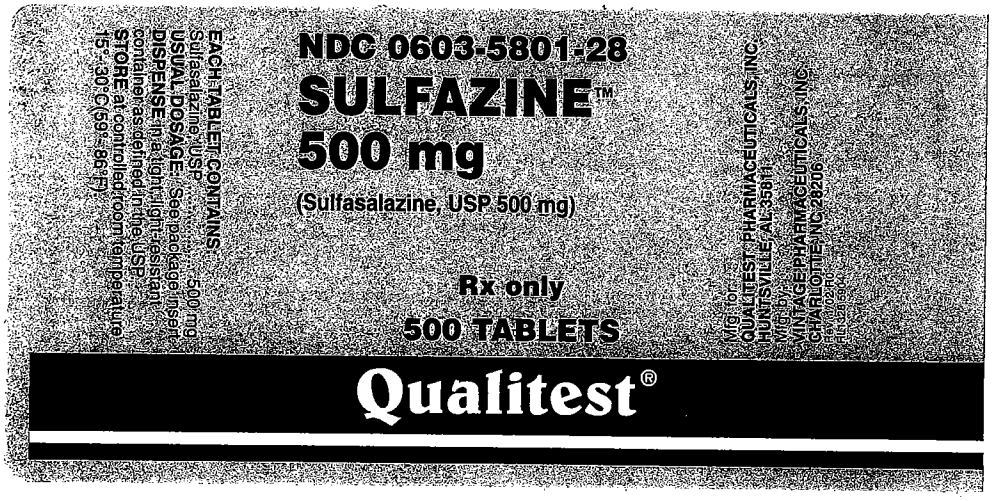


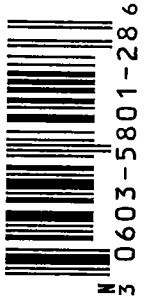
180-Count NDC# 0603-5801-04

Product Labeling

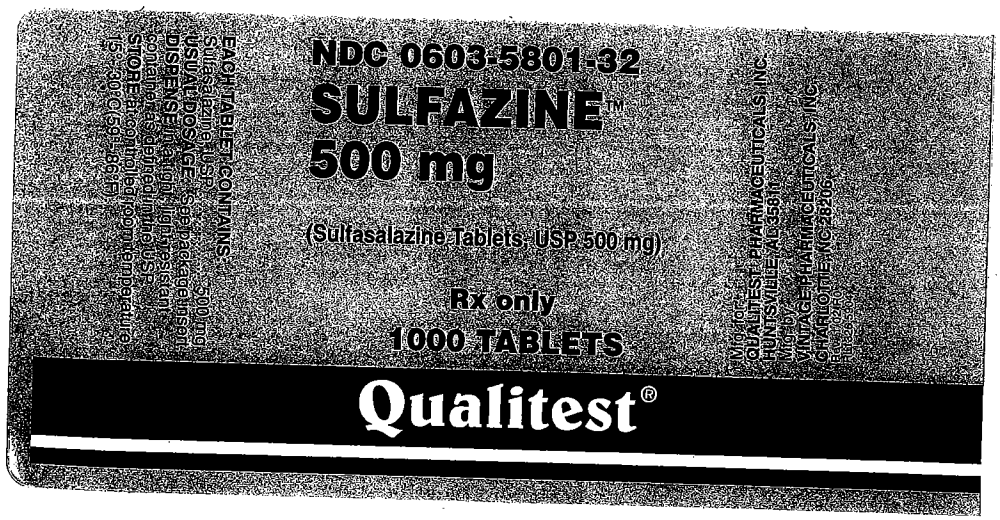
Sulfasalazine Tablets
500 mg
ANDA #40-349

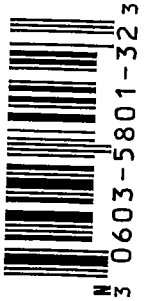
500-Count NDC# 0603-5801-28





1000-Count NDC# 0603-5801-32





CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-349

CSO LABELING REVIEW(S)

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 40-349 Date of Submission: July 27, 2000

Applicant's Name: Vintage Pharmaceuticals, Inc.

Established Name: Sulfasalazine Tablets USP, 500 mg

Labeling Deficiencies:

INSERT

a. GENERAL

Please note that USAN names are common nouns and should be treated as such in the text of labeling (*i.e.*, lower case). Upper case may be used when the USAN name stands alone as on labels or in the title of the package insert.

b. DESCRIPTION

i. Add "Molecular Weight: 398.39"

ii. Add "talc" to the list of inactive ingredients.

c. CONTRAINDICATIONS

i. Relocate "Patients hypersensitive to sulfasalazine, its metabolites, sulfonamides, or salicylates." to be the last part of the contraindication statement.

ii. Delete [redacted] from "Patients with porphyria..."

d. WARNINGS

Replace [redacted] with "central nervous system" in the second sentence.

e. PRECAUTIONS

i. Drug Interactions

Revise to read, "...reported when those agents were administered..."

ii. Carcinogenesis, Mutagenesis, Impairment of Fertility

Add a space between "chromosomal" and "aberration" in last sentence of the second paragraph.

iii. Pregnancy: Teratogenic Effects: Pregnancy Category B

(a) Revise the last two sentences of the second paragraph to read, "A study of 1,455 pregnancies associated with exposure to sulfonamides indicated that this group of drugs, including sulfasalazine, did not appear to be associated with fetal malformation.[2]" and "A review of the medical literature covering 1,155 pregnancies in women with ulcerative colitis suggested that the outcome was similar to that expected in the general population.[3]", respectively.

(b) Revise the last paragraph to read, "...sulfasalazine on the growth development and..."

f. ADVERSE REACTIONS

Replace the subsection heading "reactions" with "Central nervous system reactions".

g. DOSAGE AND ADMINISTRATION

i. Revise the first sentence of the first paragraph to read, "Dosage of sulfasalazine tablets should be adjusted to..."

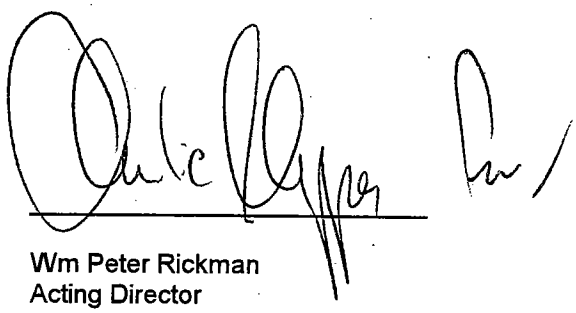
ii. Combine the second and third paragraphs.

Please revise your insert labeling, as instructed above, and submit 12 final printed copies for a full approval of this application.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes –

http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.



Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-349

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 1

2. ANDA # 40-349

3. NAME AND ADDRESS OF APPLICANT
Vintage Pharmaceuticals, Inc.
Attention: Rebecca Childers
3241 Woodpark Blvd.
Charlotte, NC 28206

4. BASIS OF SUBMISSION
Reference Listed drug product: Azulfidine Tablets[R] by Pharmacia and Upjohn approved in NDA #07-073.

According to patent certification, there are no active patents or periods of exclusivity in effect for the listed drug product.

The proposed drug product contains the same active ingredients and has same strength, dosages form, route of administration, indications and usage as the listed drug.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
[redacted]

7. NONPROPRIETARY NAME
Sulfasalazine Tablets

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
Original submission: 11-30-98
Correspondence: 12-4-98 (Response to 12-4-98 T-con)
Acknowledgement: 12-29-98

10. PHARMACOLOGICAL CATEGORY
Antiulcer

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]

13. DOSAGE FORM
Tablets

14. POTENCY
500 mg

15. CHEMICAL NAME AND STRUCTURE
Listed in labeling insert.

16. RECORDS AND REPORTS
N/A

17. COMMENTS
Chemistry - This application contains chemistry deficiencies.
Bioequivalence - Bioequivalence acceptable on 3/17/99 by C. Kim.
Labeling - Pending
EER - Submitted, awaiting results

18. CONCLUSIONS AND RECOMMENDATIONS
The application is unapprovable. Major amendment.

19. REVIEWER:
Karen A. Bernard, Ph.D.

DATE COMPLETED:
5-05-99

APPEARS THIS WAY
ON ORIGINAL

Redacted 13

Page(s) of trade secret and /or confidential commercial information

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 40-349

3. NAME AND ADDRESS OF APPLICANT
Vintage Pharmaceuticals, Inc.
Attention: Rebecca Childers
3241 Woodpark Blvd.
Charlotte, NC 28206

4. BASIS OF SUBMISSION
Reference Listed drug product: Azulfidine Tablets[R] by Pharmacia and Upjohn approved in NDA #07-073.

According to patent certification, there are no active patents or periods of exclusivity in effect for the listed drug product.

The proposed drug product contains the same active ingredients and has same strength, dosages form, route of administration, indications and usage as the listed drug.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
[redacted]

7. NONPROPRIETARY NAME
Sulfasalazine Tablets

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
Original submission: 11-30-98
Correspondence: 12-4-98 (Response to 12-4-98 T-con)
Acknowledgement: 12-29-98
Deficiency Letter: 6-15-99
Amendment Response: 6-23-99

10. PHARMACOLOGICAL CATEGORY
Antiulcer

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
DMF [redacted]
DMF [redacted]
DMF [redacted]

DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]

13. DOSAGE FORM
Tablets

14. POTENCY
500 mg

15. CHEMICAL NAME AND STRUCTURE
Listed in labeling insert.

APPEARS THIS WAY
ON ORIGINAL

16. RECORDS AND REPORTS
N/A

17. COMMENTS
Chemistry - This application contains minor chemistry deficiencies.
Bioequivalence - Bioequivalence acceptable on 3/17/99 by C. Kim.
Labeling - Pending
EER - Acceptable on 4/28/99.

18. CONCLUSIONS AND RECOMMENDATIONS
The application is unapprovable. Fax amendment.

19. REVIEWER:
Karen A. Bernard, Ph.D.

DATE COMPLETED:
11-08-99

Redacted 18

Page(s) of trade secret and /or confidential commercial information

1. CHEMISTRY REVIEW NO. 3

2. ANDA # 40-349

3. NAME AND ADDRESS OF APPLICANT
Vintage Pharmaceuticals, Inc.
Attention: Christopher J. Nascone
3241 Woodpark Blvd.
Charlotte, NC 28206

4. BASIS OF SUBMISSION
Reference Listed drug product: Azulfidine Tablets[R] by Pharmacia and Upjohn approved in NDA #07-073.

According to patent certification, there are no active patents or periods of exclusivity in effect for the listed drug product.

The proposed drug product contains the same active ingredients and has same strength, dosages form, route of administration, indications and usage as the listed drug.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
[redacted]

7. NONPROPRIETARY NAME
Sulfasalazine Tablets

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
Original submission: 11-30-98
Correspondence: 12-4-98 (Response to 12-4-98 T-con)
Acknowledgement: 12-29-98
Deficiency Letter: 6-15-99
Amendment Response: 6-23-99
Fax Deficiency Letter: 12-10-99
Amendment Response: 2-16-00

10. PHARMACOLOGICAL CATEGORY
Antiulcer

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]

DMF —— [redacted]
DMF ——
DMF ——
DMF ——
DMF ——
DMF ——
DMF ——

13. DOSAGE FORM
Tablets

14. POTENCY
500 mg

15. CHEMICAL NAME AND STRUCTURE
Listed in labeling insert.

16. RECORDS AND REPORTS
N/A

17. COMMENTS
Chemistry - Minor chemistry deficiencies remain. Fax amendment.
Bioequivalence - Bioequivalence acceptable on 3/17/99 by C. Kim.
Labeling - Pending
EER - Acceptable on 4/28/99.

18. CONCLUSIONS AND RECOMMENDATIONS
The application is unapprovable. Major amendment.

19. REVIEWER:
Karen A. Bernard, Ph.D.

DATE COMPLETED:
3-03-00

Redacted 18

Page(s) of trade secret and /or confidential commercial information

1. CHEMISTRY REVIEW NO. 4

2. ANDA # 40-349

3. NAME AND ADDRESS OF APPLICANT
Vintage Pharmaceuticals, Inc.
Attention: Christopher J. Nascone
3241 Woodpark Blvd.
Charlotte, NC 28206

4. BASIS OF SUBMISSION
Reference Listed drug product: Azulfidine Tablets[R] by Pharmacia and Upjohn approved in NDA #07-073.

According to patent certification, there are no active patents or periods of exclusivity in effect for the listed drug product.

The proposed drug product contains the same active ingredients and has same strength, dosages form, route of administration, indications and usage as the listed drug.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
[redacted]

7. NONPROPRIETARY NAME
Sulfasalazine Tablets

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
Original submission: 11-30-98
Correspondence: 12-4-98 (Response to 12-4-98 T-con)
Acknowledgement: 12-29-98
Deficiency Letter: 6-15-99
Amendment Response: 6-23-99
Fax Deficiency Letter: 12-10-99
Amendment Response: 2-16-00
Major Deficiency: 3-16-00
Amendment Response: 3-28-00

10. PHARMACOLOGICAL CATEGORY
Antiulcer

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
DMF [redacted]
DMF [redacted]

DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]

13. DOSAGE FORM
Tablets

14. POTENCY
500 mg

15. CHEMICAL NAME AND STRUCTURE
Listed in labeling insert.

16. RECORDS AND REPORTS
N/A

17. COMMENTS
Chemistry - A few chemistry issues remain. Fax amendment.
Bioequivalence - Bioequivalence acceptable on 3/17/99 by C. Kim.
Labeling - Acceptable on 12/9/99 by K. Lee.
EER - Acceptable on 4/28/99.

18. CONCLUSIONS AND RECOMMENDATIONS
The application is not approvable. ~~Fax~~ amendment.

19. REVIEWER:
Karen A. Bernard, Ph.D.

DATE COMPLETED:
7-18-00

Redacted 18

Page(s) of trade secret and /or confidential commercial information

1. CHEMISTRY REVIEW NO. 5

2. ANDA # 40-349

3. NAME AND ADDRESS OF APPLICANT
Vintage Pharmaceuticals, Inc.
Attention: Christopher J. Nascone
3241 Woodpark Blvd.
Charlotte, NC 28206

4. BASIS OF SUBMISSION
Reference Listed drug product: Azulfidine Tablets[R] by Pharmacia and Upjohn approved in NDA #07-073.

According to patent certification, there are no active patents or periods of exclusivity in effect for the listed drug product.

The proposed drug product contains the same active ingredients and has same strength, dosages form, route of administration, indications and usage as the listed drug.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME

7. NONPROPRIETARY NAME
Sulfasalazine Tablets

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
Original submission: 11-30-98
Correspondence: 12-4-98 (Response to 12-4-98 T-con)
Acknowledgement: 12-29-98
Deficiency Letter: 6-15-99
Amendment Response: 6-23-99
Fax Deficiency Letter: 12-10-99
Amendment Response: 2-16-00
Major Deficiency: 3-16-00
Amendment Response: 3-28-00
FDA Minor deficiency letter: 8-7-00
Amendment Response: 8-18-00

10. PHARMACOLOGICAL CATEGORY
Antiulcer

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
DMF —
DMF —
DMF —
DMF —
DMF —
DMF —
DMF —
DMF —
DMF —
DMF —
DMF —

13. DOSAGE FORM
Tablets

14. POTENCY
500 mg

15. CHEMICAL NAME AND STRUCTURE
Listed in labeling insert.

16. RECORDS AND REPORTS
N/A

17. COMMENTS
Chemistry - Type II DMF — is deficient. All other chemistry issues have been resolved.
Bioequivalence - Bioequivalence acceptable on 3/17/99 by C. Kim.
Labeling - Acceptable on 12/9/99 by K. Lee.
EER - Acceptable on 4/28/99.

18. CONCLUSIONS AND RECOMMENDATIONS
The application is not approvable until issues regarding DMF #2239 have been resolved. Minor amendment.

19. REVIEWER:
Karen A. Bernard, Ph.D.

DATE COMPLETED:
9-6-00

Redacted 19

Page(s) of trade secret and /or confidential commercial information

1. CHEMISTRY REVIEW NO. 6

2. ANDA # 40-349

3. NAME AND ADDRESS OF APPLICANT
Vintage Pharmaceuticals, Inc.
Attention: Christopher J. Nascone
3241 Woodpark Blvd.
Charlotte, NC 28206

4. BASIS OF SUBMISSION
Reference Listed drug product: Azulfidine Tablets[R] by Pharmacia and Upjohn approved in NDA #07-073.

According to patent certification, there are no active patents or periods of exclusivity in effect for the listed drug product.

The proposed drug product contains the same active ingredients and has same strength, dosages form, route of administration, indications and usage as the listed drug.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME

7. NONPROPRIETARY NAME
Sulfasalazine Tablets

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
Original submission: 11-30-98
Correspondence: 12-4-98 (Response to 12-4-98 T-con)
Acknowledgement: 12-29-98
Deficiency Letter: 6-15-99
Amendment Response: 6-23-99
Fax Deficiency Letter: 12-10-99
Amendment Response: 2-16-00
Major Deficiency: 3-16-00
Amendment Response: 3-28-00
FDA Minor deficiency letter: 8-7-00
Amendment Response: 8-18-00
Minor Deficiency: 9-15-00
Amendment Response: 10-11-00
Telephone amendment: 11-7-00
Telephone amendment: 11-21-00

10. PHARMACOLOGICAL CATEGORY
Antiulcer

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]
DMF [redacted]

13. DOSAGE FORM
Tablets

14. POTENCY
500 mg

15. CHEMICAL NAME AND STRUCTURE
Listed in labeling insert.

16. RECORDS AND REPORTS
N/A

17. COMMENTS
Chemistry - Type II DMF [redacted] is now adequate. All other chemistry issues have been resolved.
Bioequivalence - Bioequivalence acceptable on 3/17/99 by C. Kim.
Labeling - Acceptable on 12/9/99 by K. Lee.
EER - Acceptable on 4/28/99.

18. CONCLUSIONS AND RECOMMENDATIONS
The application is approvable.

19. REVIEWER:
Karen A. Bernard, Ph.D.

DATE COMPLETED:
11-7-00

Redacted 21

Page(s) of trade secret and /or confidential commercial information

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-349

BIOEQUIVALENCE REVIEW(S)

Sulfasalazine Tablets, USP
500 mg
ANDA #40349
Reviewer: Carol Y. Kim
v:\new\firmsnz\vintage\ltrs&rev\40349SD.n98.doc

Vintage Pharmaceuticals, Inc.
Charlotte, NC
Submission Date:
November 30, 1998
February 9, 1999

Review of Two Bioequivalence Studies and Dissolution Data

I. Introduction

Class: Anti-inflammatory agent

RLD: Azulfidine[R] Tablets, 500 mg, Pharmacia & Upjohn Co.

Recommended Dose: Initial dose- 3-4 g/daily, Maintenance dose- 2 g/day

II. Objectives

Review of:

- Two-way crossover in vivo bioequivalence study comparing Vintage Pharmaceutical, Inc.'s Sulfasalazine Tablets, USP, 500 mg to Pharmacia & Upjohn's Azulfidine[R] (Sulfasalazine Tablets, USP), 500 mg strength.
- In vitro dissolution data for 500 mg tablets.

III. Background

Sulfasalazine is used in the treatment of ulcerative colitis and Crohn's disease.

Sulfasalazine is synthesized by diazotization of sulfapyridine and coupling of the diazonium salt with salicylic acid. It is considered as a prodrug since the diazo bond is cleaved in vivo to provide sulfapyridine and 5-aminosalicylic acid (mesalamine). Following an oral administration of a single 2 g of sulfasalazine, peak serum concentrations occur within 1.5-6 hours and average 14 ug/ml. Peak serum sulfapyridine concentrations occur within 6-24 hours and average 21 ug/ml. Mean serum half-life of sulfasalazine is 5.7 hours following a single dose of 4 g doses whereas for sulfapyridine, it is 8.4 hours. Most of the dose of sulfasalazine is excreted in the urine.

III. Protocols No. 9727014 and 9727022: A single-dose, 2-way crossover randomized study under fasting conditions:

Note: Since the fasting study (#9727014) failed the two one sided test criterion due to aberrant values of subject #10, the firm conducted another fasting study (#9727022) repeating subject #10 and two other subjects (#15, #24) from the previous study (#9727014).

A. Study information

Study facility information:

Clinical Site:	[redacted]	
Investigator:	[redacted]	
Analytical Site:	[redacted]	
Analytical Director:	[redacted]	
	#9727014	**#9727022**
Study Dates:	Period #1: 10/18-10/21/97 Period #2: 11/1-11/4/97	Period #1: 1/31-2/3/98 Period #2: 2/14-2/17/98
Analysis Dates:	11/10-11/23/97	2/25-2/27/98
Storage Period:	no > 37 days at -20°C	no > 28 days at -20°C

Study design:

Protocol No.:	9727014 & 9727022
Design Type:	two-way crossover
Randomized:	Y
Single or Multiple dose:	single
No. of Treatment:	2
No. of Periods:	2
No. of Sequences:	2
Washout Period:	14 days

Subjects:

Normal Healthy Volunteers:	Y	
IRB Approval:	Y	
Informed Consent	Y	
No. of Subjects Enrolled:	**#9727014**	**#9727022**
	Entered: 26 males	3 males
	Completed: 23 males	3 males
	Excluded from analysis: 3 males	none
Age:	19-55 years	21-51 years
Inclusion/Exclusion Criteria:	listed in vol. 1.2, pp. 101-102	vol. 1.2, pp. 126-127
Housing:	Evening prior to each drug administration until after 36 hours post dose.	

Treatment information:

Treatment:	A	B
Test or Reference:	Test	Reference

Product Name:	Sulfasalazine Tablet	Azulfidine[R] Tablet
Strength:	500 mg	500 mg
Manufacturer:	Vintage	Pharmacia & Upjohn
Lot No.:	#097066A	#XK3195B
Assay:	96.7 %	100.1 %
Content Uniformity (% CV):	96.5 % (1.7)	100.1 % (0.5)
Batch Size (ANDA/Full):		
Expiration Date:	5/98	9/99
Dose Administered:	4 X 500 mg	4X 500 mg
Length of Fasting:	10 hours	10 hours

Dosing:

Subjects fasted overnight before dosing and for at least 2 hours after dosing. Each oral dose was administered with 240 ml of water. Standard meals or snack were provided at 4, 10, 14, 24, 28, and approximately 34 hours after dosing.

Blood Sampling:

Blood sample volume	10 ml
No. of time points	17
Time points:	0, 1,2,3,4,5,6,8,10,12,14,16,24,30,36,48 and 72 hours post dose

The plasma samples were stored at –19° C (#9727022) and –17°C (#9727014) until analysis, respectively

B. Study Results

1. Clinical

Drop-outs: -Subject #1 and #21 did not return for Period II for personal reasons. Subject #24 did not complete due to serious adverse event, broken arm. (#9727014)
-none from #9727022 study

Adverse events: : -Total- 4 adverse events in association to the study drug (#9727014)
-2 events (2 subjects)-treatment A
-1 event (1 subject)-treatment B
-Remaining 1 event was unrelated to the study drug. (vol. 1.2, p. 149)
-Common adverse event: mild headache
-none from #9727022 study

2. Analytical Methodology (The following section is not to be released under FOI)

Method:

Internal Standard:
Specificity:

Linearity:
Sensitivity:
Quality Control (QC)

Protocol Deviations: none other than minor sampling deviations in both studies.

Conclusion: **Analytical method is acceptable**

3. Pharmacokinetic/Statistical Analysis

Mean Sulfapyridine plasma levels of 23 subjects are summarized in Table 1a, individual plasma levels of 3 subject's side by side comparison (#10, #15, and #24) in Table 1b, and mean plasma levels of 22 subjects (excluding outlier-#10) in Table 1c.

Table 1a: Mean Sulfapyridine Plasma Concentrations including subject #10 for test and reference products (N=23)

	Sulfasalazine Tablet : Test Lot# 097066A		Sulfasalazine Tablet: Reference Lot # XK3195B		Ratio
Time (hour)	Mean (ug/ml)	CV %	Mean (ug/ml)	CV %	T/R*
0	0.0	-	0.0	-	0.00
1	0.0096	479.6	0.0	-	0.00
2	0.0366	343.1	0.2652	379.6	0.14
3	0.1795	301.9	0.5698	224.4	0.32
4	0.8448	236.3	1.3776	177.5	0.61
5	2.8899	124.6	3.5268	102.3	0.82
6	5.5949	79.8	6.6722	72.6	0.84
8	8.6265	54.3	10.1952	52.4	0.85
10	9.7448	47.2	11.8296	44.5	0.82
12	10.2948	45.6	12.0243	40.6	0.86
14	10.2496	47.1	11.3922	41.4	0.90
16	9.6704	47.5	10.7648	44.1	0.90
24	7.2420	63.8	7.6193	61.0	0.95
30	4.9240	73.4	5.4794	74.0	0.90
36	3.5872	85.6	3.9148	84.0	0.92
48	2.0158	104.7	2.1930	104.7	0.92
72	0.6210	147.4	0.7060	140.0	0.88

*Calculated by the reviewer

Table 1b: Side by side comparison of individual plasma concentrations for #9727014 (original) and #9727022 (repeated subjects) for test and reference products (N=3)

Repeated Study #9727022 (subjects #10, 15, 24)							Original Study # 9727014 (subjects #10, 15, 24)					
Time (hour)	#10 (A)	#10 (B)	#15 (A)	#15 (B)	#24 (A)	#24 (B)	#10 (A)	#10 (B)	#15 (A)	#15 (B)	#24 (A)	#24 (B)
0												
1												
2												
3												
4												
5												
6												
8												
10												
12												
14												
16												
24												
30												
36												
48												
72												

A: Test; B: Reference

Table 1c: Mean Sulfapyridine Plasma Concentrations excluding subject #10 for test and reference products (N=22)

	Sulfasalazine Tablet : Test Lot# 097066A		Sulfasalazine Tablet: Reference Lot # XK3195B		Ratio
Time (hour)	Mean (ug/ml)	CV %	Mean (ug/ml)	CV %	T/R*
0	0.0	-	0.0	-	0.00
1	0.01	469.0	0.0	-	0.00
2	0.0383	335.2	0.0681	371.0	0.56
3	0.1876	294.8	0.5957	218.7	0.31
4	0.8832	230.4	1.4349	173.3	0.62
5	3.0004	121.5	3.3712	107.2	0.89
6	5.8073	76.6	6.2936	73.0	0.92
8	8.9541	50.4	9.7723	51.8	0.92
10	10.1036	43.2	11.5082	44.7	0.88
12	10.6564	41.9	11.7755	41.2	0.90
14	10.5709	44.3	11.1964	42.3	0.94
16	9.9195	45.7	10.5541	45.0	0.94
24	7.3539	63.8	7.4930	63.0	0.98
30	4.9978	73.7	5.3639	76.6	0.93
36	3.6494	85.8	3.8268	87.2	0.95
48	2.0556	104.7	2.1545	108.7	0.95
72	0.6376	146.6	0.7016	144.1	0.91

Analysis of variance was performed on each pharmacokinetic parameter using SAS proc GLM. Mean reported pharmacokinetic parameters for Sulfapyridine are shown in Table 2. Side by side comparison of individual pharmacokinetic parameters for subjects #10, 15, and 24 are shown in Table 3. The LS means of the ln-transformed pharmacokinetic parameters, means, and the 90% confidence intervals of test product versus reference product are presented in Table 4.

Table 2: Test mean/Reference mean ratios of pharmacokinetic parameters

a. Sulfapyridine (N=23) (#9727014)						**b. Sulfapyridine (N=22) (#9707014)**				
Parameter*	Test Mean	CV %	Ref Mean	CV %	Ratio (T/R)[1]	Test Mean	CV %	Ref Mean	CV %	Ratio (T/R)[1]
AUCT	290.1458	62.0	327.7963	57.0	0.89	297.0889	60.9	320.5288	58.6	0.93
AUCI	313.3289	67.2	332.5219	60.7	0.94	321.1177	66.0	324.4254	62.6	0.99
CMAX	11.6904	37.5	13.6335	33.3	0.86	12.0045	35.1	13.3668	33.4	0.90
KE	0.0781	49.5	0.0789	34.9	0.99	0.0789	49.8	0.0800	45.3	0.99
T ½	11.2087	49.3	10.7886	45.5	1.04	11.1880	50.6	10.6906	49.2	1.05
TMAX	13.0442	28.4	12.7826	33.3	1.02	12.5462	23.2	13.0000	34.2	0.97

*AUCT=ug*hr/ml, AUCI=ug*hr/ml, TMAX=hr, CMAX=ug/ml

[1]Calculated by reviewer

Table 3: Side by side comparison of individual pharmacokinetic parameters for #9727014 (original) and #9727022 (repeated subjects) for test and reference products (N=3)

Parameter	#9727022 (repeated) Test	#9727022 (repeated) Reference	T/R	#9727014 (original) Test	#9727014 (original) Reference	T/R
Subject #10						
AUCT	437.56	448.02	0.98	137.40	487.68	0.28
AUCI	454.77	460.01	0.99	141.98	502.55	0.28
CMAX	18.70	19.90	0.94	4.78	19.50	0.25
TMAX	12.00	10.00	1.20	24.00	8.00	3.00
KE	0.05	0.06	0.83	0.06	0.05	1.20
$T_{1/2}$	14.40	12.44	1.16	11.67	12.85	0.91
Subject #15						
AUCT	131.41	119.47	1.10	156.60	158.24	0.99
AUCI	133.43	120.95	1.10	160.08	161.87	0.99
CMAX	7.03	6.96	1.01	9.59	9.36	1.02
TMAX	12.00	12.00	1.00	12.00	10.00	1.20
KE	0.11	0.11	1.00	0.10	0.09	1.11
$T_{1/2}$	6.45	6.31	1.02	7.10	7.40	0.96
Subject #24						
AUCT	109.30	101.14	1.08	106.74	117.08	0.91
AUCI	110.79	102.71	1.08	107.99	118.87	0.91
CMAX	6.71	7.26	0.92	7.14	7.44	0.96
TMAX	12.00	12.00	1.00	12.00	12.00	1.00
KE	0.12	0.11	1.09	0.11	0.11	1.00
$T_{1/2}$	5.91	6.24	0.95	6.22	6.55	0.95

*AUCT=ug*hr/ml, AUCI=ug*hr/ml, TMAX=hr, CMAX=ug/ml
[1]Calculated by reviewer

Table 4: LSMeans and 90% confidence intervals for Sulfasalazine Tablet

#9727014	Sulfapyridine (n=23)		**Sulfapyridine (n=22)**		Sulfapyridine (n=23)		**Sulfapyridine (n=22)**	
Parameter*	LS Means (test)	LS Means (ref)	LS Means (test)	LS Means (ref)	Low CI (%)**	Upper CI (%)**	Low CI (%)**	Upper CI (%)**
AUCI	314	349	322	342	78.35	95.97	87.8	95.1
AUCT	290	328	298	320	78.24	95.43	87.9	95.6
CMAX	11.7	13.6	12.0	13.3	74.29	94.75	82.4	96.1

*AUCT=ug*hr/ml, AUCI=ug*hr/ml, CMAX=ug/ml
**Used natural log transformed parameter

Table 5: Total S.D. and Root Mean Square Error (MSE) for ln-transformed AUCT and CMAX

	#9727014 (n=23)		#9727014 (n=22)	
	ln AUCT	ln CMAX	ln AUCT	ln CMAX
Total SD Test	0.6540264	0.3988257	0.6579408	0.6199745
Total SD Reference	0.6182353	0.3315793	0.6199745	0.3268167
MSE Test & Reference	0.19568423	0.23973210	0.07705649	2.48298627

Comments

1. Subject #10 showed extremely low rate of absorption in period 2 (test) in study #9727014. The firm then conducted a repeat study (#9727022) with subject #10 and two other subjects chosen at random from those who completed #9727014 study. The firm substituted these data for the original data, repeated statistical analysis, and presented the combined data.

2. DBE does not allow the substitution of repeated subjects in the second study (#9727022). In the repeat study #9727022 (n=3), pharmacokinetic parameters of test and reference products for subject #10 were similar to each other (T/R ratios close to 1.0) and to respective mean values from study #9727014. The individual pharmacokinetic parameters for subjects #15 and #24 in the repeat study were comparable to corresponding values in the original study. For subject #10, AUCT, AUCI, and CMAX levels following test treatment in study #9727014 were considerably lower than RLD, and test TMAX was two times higher than reference TMAX. The results of study #9727022 confirm that subject #10 was aberrant and had a bad test day when originally dosed with test product in period 2 of study #9727014. Thus, it is acceptable to drop subject #10 from statistical data analysis of study #9727014.

3. The 90% confidence intervals of ln-transformed AUCT, AUCI, and CMAX ratios for Sulfapyridine in study #9727014 (n=22) are all within 80-125% range.

4. There were no statistically significant period or sequence effects for LCMAX, LAUCT and LAUCI in study #9727014 (n=22). ($p>0.05$) Although significant period effect on LAUCT was noted, the reviewer concluded that this does not have an impact on the study outcome.

5. The mean (%CV) AUC_T/AUC_I ratios of Sulfapyridine (#9727014, n=22) were 0.95 (5.2), range 0.79 to 0.99, and 0.96 (4.1), range 0.82 to 0.99, for test and reference, respectively.

6. Kel and AUCI could not be determined for subject #9 in the study. The reviewer concurs with this observation.

7. The pharmacokinetic parameters and 90% confidence intervals re-calculated by the reviewer were in good agreement with the values determined by the firm.

Conclusion: The study is acceptable.

VI. Dissolution

Method of dissolution	USP 23, Apparatus I (basket)
Speed	100 rpm
No. of Units Tested	12
Medium	pH 7.5 Phosphate Buffer
Temperature	37°C
Volume	900 ml
Specifications	NLT 85% (Q) is dissolved in 60 minutes
Assay Methodology	
Reference Product	Azulfidine^{R} Tablet, 500 mg

Result of In Vitro Dissolution Profile Summary for Sulfasalazine 500 mg

Sampling Times (minutes)	Sulfapyridine Tablets (Test) Lot # 097066 Strength: 500 mg			Azulfidine^{R} Tablets (Ref) Lot #XK3195B Strength: 500 mg		
	Mean %	Range	%CV	Mean %	Range	%CV
15	55.0		3.7	95.4		2.6
30	95.2		1.5	99.8		0.8
45	99.1		1.7	100.3		0.7
60	99.5		1.8	100.5		0.8

Comment

The firm conducted dissolution according to the procedure described in the USP 23. The dissolution data are acceptable.

VII. Composition of Formulation

Composition of Vintage's Sulfasalazine Tablets (Not to Be Released Under FOI)

Ingredients	**Sulfasalazine Tablets, USP, 500 mg (per tablet)**
Sulfasalazine, USP	500.00 mg
Partially Pregelatinized Starch, NF	
Polyvinyl Pyrilidone.	
Croscramellose Sodium, NF	
Microcrystalline Cellulose,	
Corn Starch, NF	
Talc, USP	
Magnesium Stearate, NF	
*Polyvinyl Pyrilidone,	
*Purified Water	
Total	680.00 mg

VIII. Recommendations

1. The single-dose bioequivalence study, #9727014 (n=22), under fasting conditions, conducted by Vintage Pharmaceuticals Inc. on its Sulfasalazine Tablet, USP, 500 mg, lot #097066A, comparing it to Azulfidine^{R} 500 mg, lot #XK3195B, manufactured by

Pharmacia & Upjohn Co., has been found acceptable by the Division of Bioequivalence. The study demonstrates that Vintage Pharmaceutical's Sulfasalazine Tablet, USP, 500 mg is bioequivalent to Pharmacia & Upjohn's Azulfidine[R] Tablet, 500 mg.

2. The dissolution testing conducted by Vintage Pharmaceuticals Inc. on its Sulfasalazine Tablets, 500 mg (lot #097066A) is acceptable. The Division of Bioequivalence deems Sulfasalazine, 500 mg, to be bioequivalent to Azulfidine[R] Tablets, 500 mg.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. Dissolution testing should be conducted in 900 ml of pH 7.5 phosphate buffer at 37°C using USP 23 Apparatus I (basket) at 100 rpm. The test should meet the following specification:

> Not less than 85% (Q) of the labeled amount of the drug in the dosage form is dissolved in 60 minutes.

The firm should be informed of the recommendations.

Carol Y. Kim, Pharm.D.
Division of Bioequivalence
Review Branch III

BDavit 3/12/99

RD INITIALLED BY BDAVIT
FT INITIALLED BY BDAVIT Barbara N Davit Date: 3/16/99

Concur: Dale P. Conner Date: 3/17/99
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

APPEARS THIS WAY
ON ORIGINAL

CC: ANDA #40349
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-658/ Reviewer C. Kim
HFD-658/ Bio team leader B. Davit

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Endorsements: (Final with Dates)
HFD-658/ Reviewer C. Kim 3/15/99
HFD-658/ Bio team Leader B. Davit 3/16/99
HFD-617/ Project Manager 3/19/99
HFD-650/ D. Conner 3/17/99

BIOEQUIVALENCY - ACCEPTABLE Submission date: 11/30/98

1. **Fasting Study #1 (9727014, n=22)(STF)** **Strength: 500 mg**

   Clinical: **Outcome: AC**
   Analytical:

2. ~~**Fasting Study**~~ **#2 (9727022)(STF)** **Strength: 500 mg**
   OTHER
   Clinical: **Outcome: NA**
   Analytical:

3. **Study Amendment (STA)** **Strength: 500 mg**
   February 9, 1999 **Outcome: AC**

Outcome Decisions: **AC** - Acceptable
NA - Not acceptable

WinBio Comments: Fasting Study #1 -Unacceptable
Fasting Study #2 -Acceptable
Dissolution -Acceptable

APPEARS THIS WAY
ON ORIGINAL

Fig. 1A: Mean plasma concentration of sulfapyridine (including subj. #10, #9727014)

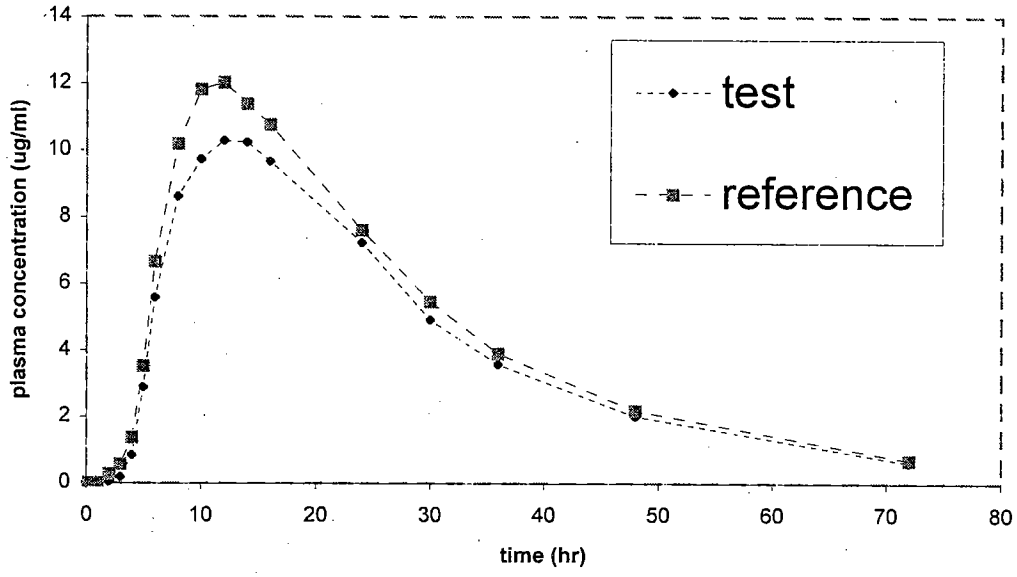
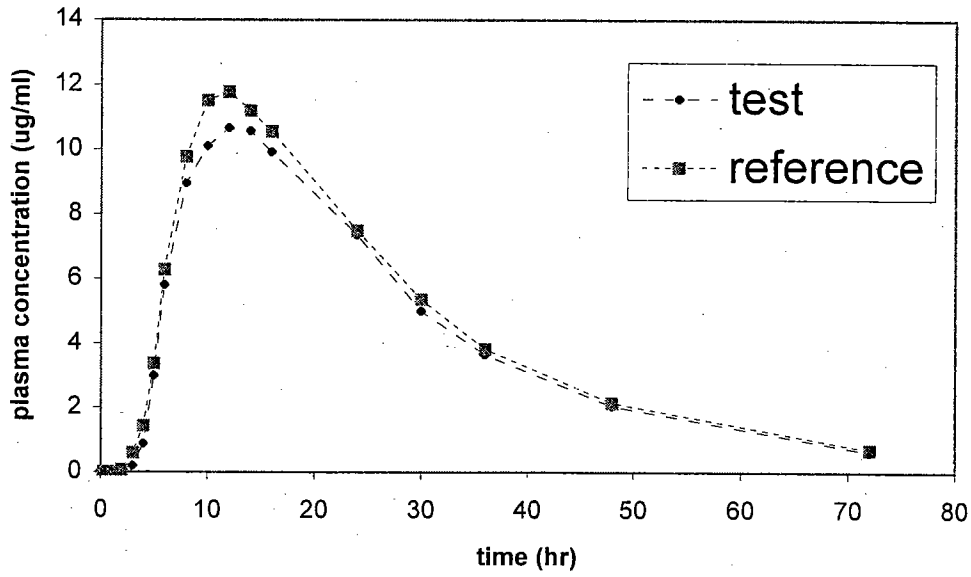


Fig. 1B: Mean plama concentration of sulfapyridine (excluding subj. #10, #9727014)



BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT
ANDA: #40349 APPLICANT: Vintage Pharmaceuticals Inc.

DRUG PRODUCT: Sulfasalazine Tablets, USP, 500 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

The dissolution testing will need to be incorporated into your stability and quality control programs.

The Division of Bioequivalence is presently evaluating the criteria by which bioequivalence of Sulfasalazine drug products will be determined. Current practices may be changed in the near future.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

OFFICE OF GENERIC DRUGS

DIVISION OF BIOEQUIVALENCE

ANDA # 40-349 SPONSOR: Vintage Pharmaceuticals, Inc.

DRUG & DOSAGE FORM: Sulfasalazine Tablets, USP

STRENGTH (S): 500 mg

TYPE OF STUDY: SD X SDF MULT OTHER

STUDY SUMMARY: In a single dose fasting BE study, Sulfasalazine Tablets, USP (500 mg) was shown to be bioequivalent to Azulfidine[R] (500 mg).

Formulation is acceptable, waiver is granted

PRIMARY REVIEWER: Carol Y. Kim BRANCH: 3
INITIAL: Carol Y. Kim DATE: 3/15/99

TEAM LEADER: Barbara M. Davit BRANCH: 3
INITIAL: Barbara M. Davit DATE: 3/16/99

DIRECTOR
DIVISION OF BIOEQUIVALENCE
INITIAL: _____ DATE: 3/16/99

DIRECTOR
OFFICE OF GENERIC DRUGS
INITIAL: _____ DATE: _____

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-349

ADMINISTRATIVE DOCUMENTS

Telephone Conversation Memorandum

ANDA: 40-349

DRUG: Sulfasalazine Tab USP, 500 mg

FIRM: Vintage

PERSONS INVOLVED: Regina Henry; Pan Troxler; Vintage Pharmaceuticals.
Vilayat A. Sayeed, Ph.D.; Office of Generic Drugs

PHONE NUMBER: 704 596-0516

DATE: 11/21/2000

Called the firm and requested to clarify the discrepancy in the total impurities limits. A limit of — is submitted in the submission of 8/18/2000, where as the submission of 11/7/2000 lists the limit as — Firm acknowledged the discrepancy and volunteered to provide a revised stability protocol with a limit of — limit for total impurities.

Firm was requested to revise the protocol and submit the information as a telephone amendment.

Vilayat Sayeed, Ph.D.
Deputy Directory, Div Chem II, OGD

Vilayat Sayeed

cc: ANDA 40-349
Division file (1)

File: V:\firmsnz\vintage\telecons\40349nov21.2000.doc

APPEARS THIS WAY
ON ORIGINAL

DIVISION REVIEW SUMMARY

ANDA: 40-349

DRUG PRODUCT: Sulfasalazine Tablets, USP

FIRM: Vintage Pharmaceutical Co.

DOSAGE FORM: Tablets

STRENGTH: 500 mg

CGMP STATEMENT/EIR UPDATE STATUS:
EER Acceptable 4/28/99.

BIO INFORMATION:
The Division of Bioequivalence have found the application to be acceptable on 3/17/99 by C. Kim.

VALIDATION-DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S)
USP product, methods validation not needed.
Drug Sobstance-Compendial

Sulfasalazine Drug Product

The USP assay method is a [redacted] method which is not stability indicating. The firm has developed their own [redacted] assay method based on the drug substance supplier's method. The [redacted] method developed is stability indicating, uses a [redacted] system including an [redacted]. The applicant included the results of forced degradation studies to illustrate the stabilty indicating method.

The USP does not include a Related Compounds/Impurities specification for the tablets. The firm established their own related compounds test based on the [redacted] assay method with some revisions. The dissolution method also employed the [redacted] method for testing. All methods were validated and USP Sulfasalazine reference standard was used.

STABILITY-ARE CONTAINERS USED IN THE STUDY IDENTICAL TO THOSE USED IN THE CONTAINER SECTION?

The future stability protocol the firm proposes is as follows:

Test	Limit
Appearance	Meets Description
*Hardness	[redacted]
Assay USP	95.0%-105.0%
*Moisture	NMT [redacted]
Dissolution USP	NLT 85% (Q) in 60 min.
*Impurity Limit Tests	
Impurity X	NMT [redacted]
Impurity Y	NMT [redacted]
[redacted]	NMT [redacted] %
Related Substances	
Other Impurities	NMT [redacted] %
Total Impurities	NMT [redacted] %

The firm included 3 months of accelerated data at 40°C/75% RH for lot #097066. Data for both container configurations (100 and 1000 fill) were included, the 500 fill they propose is bracketed. The firm did not submit any room temperature data, but they will test future room temperature stability at 25-30°C, ambient humidity. The firm proposes an 24 month expiration dating period.

Also included is a future stability commitment in accordance with FDA Guidelines.

LABELING
The labeling review is satisfactory as of 12/9/99 by K. Lee.

STERILIZATION VALIDATION
NA

SIZE OF DEMONSTRATION BATCH

A description of the manufacturing process is included on page 2055.

Division Summary manufacturing process

Redacted 1

Page(s) of trade secret and /or confidential commercial information

configuration [redacted] reconciled). Total [redacted] showed [redacted] with [redacted] tablets packaged out of [redacted] tablets manufactured.

PROPOSED PRODUCTION BATCH-MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?

See above.

RECOMMENDATION: Approve

SIGNATURE: K Bernard 11/14/00 DATE: 7/18/00

B Yonemine 11/16/00

V:\Firmsnz\vintage\ltrs&rev\40-349DS.DOC

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-349

CORRESPONDENCE

3241 Woodpark Boulevard
Charlotte, NC 28206

Vintage
Pharmaceuticals, Inc.

Phone (704) 596-0516
Fax (704) 598-6237

December 13, 2001

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

ORIG AMENDMENT
N/AM

Re: ANDA# 40-349
Sulfasalazine Tablets, USP
500 mg
Minor Amendment

In accordance with Section 505(j) of the FD&C Act, as amended, and 21 CFR Part 314.94, we are submitting an amendment to the original Abbreviated New Drug Application for the above product.

This amendment is in response to a not approvable letter dated November 30, 2000. On December 10, 2001, Vintage representatives met with representatives of the FDA's Atlanta District office and were informed that the Atlanta District now considered Vintage's Charlotte, NC manufacturing facility to be in essential compliance with cGMP regulations. Vintage was also informed that the Atlanta District would recommend approval of Vintage's pending applications.

The archival copy of the amendment consists of one volume. The review copy consists of one red-jacketed chemistry & manufacturing volume and one separately bound, orange-jacketed bioequivalence volume. The following items are included immediately following the NDA Form 356h:

-Field Copy Certification

We look forward to your early response. If you have any questions or comments regarding this amendment, please contact the undersigned, or as an alternate, Ms. Fran Hutchins, Plant Manager, at Tel. (704) 596-0516.

Sincerely,
VINTAGE PHARMACEUTICALS, INC.

CJNascone

Christopher J. Nascone
Regulatory Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH
DFOI
DEC 14 2001
OGD

ANDA 40-349

Vintage Pharmaceuticals, Inc.
Attention: Christopher J. Nascone
3241 Woodpark Blvd.
Charlotte, NC 28206

NOV 30 2000

Dear Sir:

This is in reference to your abbreviated new drug application dated November 30, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Sulfasalazine Tablets USP, 500 mg.

Reference is also made to your amendments dated February 9, 1999; and October 11, November 7, and November 21, 2000.

We have completed the review of this abbreviated application and have concluded that this application is deficient and, therefore, not approvable under 21 CFR 314.125 (b)(13) because the Center for Drug Evaluation and Research (CDER) is unable to find that the methods used in, and the facilities and controls used for, the manufacture, processing, packaging or holding of the drug product, sulfasalazine tablets, by Vintage Pharmaceuticals Inc. at Charlotte, NC comply with current good manufacturing practice (cGMP) regulations.

Our conclusion is based upon a recommendation we received from our Division of Manufacturing and Product Quality (DMPQ), Office of Compliance, to withhold approval of your abbreviated application.

Until such time that you can demonstrate to the Agency that the problems have been corrected and the Agency's concerns are otherwise satisfied, your application cannot be approved.

You should amend this application when the CGMP-related issues have been satisfactorily resolved. Your amendment to the application submitted in response to this not approvable letter will be considered a MINOR AMENDMENT provided that the amendment contains no significant additional information necessary to

remedy the cGMP problems. Please include a statement from a responsible corporate official certifying that your facilities have been found to be in compliance with cGMPs and have been cleared for approval of the drug product by representatives of the local FDA District Office. If, as a result of follow-up inspections related to the ongoing evaluation of this or other applications, it is necessary for you to significantly revise your procedures, controls or practices to correct the deficiencies, then the amendment will be considered to represent a MAJOR AMENDMENT. Your amendment should be plainly marked as such in your cover letter.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120, which will either amend or withdraw this application. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

11/30/00

3241 Woodpark Blvd.
Charlotte, NC 28206

Vintage
Pharmaceuticals, Inc.

(704) 596-0516

November 21, 2000

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

NEW CORRESP
NC to
Fax

Re: ANDA # 40-349
Sulfasalazine Tablets, USP
500 mg
Telephone Amendment

In accordance with Section 505(j) of the FD&C Act, as amended, and 21 CFR Part 314.94, we are submitting an amendment to the original Abbreviated New Drug Application for the above product.

This amendment is in response to a telephone request on November 21, 2000 from Dr. Vilayet Sayeed of FDA and consists of revised accelerated stability protocols (the impurities limits has been revised to NMT —.

The archival copy of the amendment consists of one volume. The review copy consists of one red-jacketed chemistry & manufacturing volume and one separately bound, orange-jacketed bioequivalence volume. The following items are included immediately following the NDA Form 356h:

- Field Copy Certification

We look forward to your early response. If you have any questions or comments regarding this amendment, please contact the undersigned, or as an alternate, Ms. Fran Hutchins, Plant Manager, at Tel. (704) 596-0516.

Sincerely,
VINTAGE PHARMACEUTICALS, INC.

C J Nascone

Christopher J. Nascone
Regulatory Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
DEC 12 2000
OGD

3241 Woodpark Blvd.
Charlotte, NC 28206

Vintage
Pharmaceuticals, Inc.

(704) 596-0516

November 7, 2000

NDA ORIG AMENDMENT
N/Am

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

Re: ANDA# 40-349
Sulfasalazine Tablets, USP
500 mg
Telephone Amendment

In accordance with Section 505(j) of the FD&C Act, as amended, and 21 CFR Part 314.94, we are submitting an amendment to the original Abbreviated New Drug Application for the above product.

This amendment is in response to a telephone request on November 7, 2000 from Karen Bernard of FDA and consists of revised accelerated stability protocols (the hardness range has been revised to

The archival copy of the amendment consists of one volume. The review copy consists of one red-jacketed chemistry & manufacturing volume and one separately bound, orange-jacketed bioequivalence volume. The following items are included immediately following the NDA Form 356h:

-Field Copy Certification

We look forward to your early response. If you have any questions or comments regarding this amendment, please contact the undersigned, or as an alternate, Ms. Fran Hutchins, Plant Manager, at Tel. (704) 596-0516.

Sincerely,
VINTAGE PHARMACEUTICALS, INC.

C J Nascone

Christopher J. Nascone
Regulatory Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
NOV - 9 2000
OGD

3241 Woodpark Blvd.
Charlotte, NC 28206

Vintage
Pharmaceuticals, Inc.

(704) 596-0516

NDA ORIG AMENDMENT
N/Am1

October 11, 2000

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

Re: ANDA# 40-349
Sulfasalazine Tablets, USP
500 mg
Minor Amendment

In accordance with Section 505(j) of the FD&C Act, as amended, and 21 CFR Part 314.94, we are submitting an amendment to the original Abbreviated New Drug Application for the above product.

This amendment is in response to a minor deficiency letter dated September 15, 2000 from Ms. Kassandra Sherrod.

The archival copy of the amendment consists of one volume. The review copy consists of one red-jacketed chemistry & manufacturing volume and one separately bound, orange-jacketed bioequivalence volume. The following items are included immediately following the NDA Form 356h:

-Field Copy Certification

We look forward to your early response. If you have any questions or comments regarding this amendment, please contact the undersigned, or as an alternate, Ms. Fran Hutchins, Plant Manager, at Tel. (704) 596-0516.

Sincerely,
VINTAGE PHARMACEUTICALS, INC.

CJ Nascone

Christopher J. Nascone
Regulatory Affairs

CENTER FOR DRUG
REC'D
OCT 12 2000
OGD
EVALUATION AND RESEARCH

NDA 10/16/00

3241 Woodpark Blvd.
Charlotte, NC 28206

Vintage
Pharmaceuticals, Inc.

(704) 596-0516

August 18, 2000

NDA ORIG AMENDMENT
N/Am

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

Re: ANDA# 40-349
Sulfasalazine Tablets, USP
500 mg
Minor Amendment

In accordance with Section 505(j) of the FD&C Act, as amended, and 21 CFR Part 314.94, we are submitting an amendment to the original Abbreviated New Drug Application for the above product.

This amendment is in response to a fax deficiency letter dated August 7, 2000 from Ms. Kassandra Sherrod, and contains our responses to the deficiencies as well as revisions to our package insert for the above product. Final printed copies of the package inserts are also included.

The archival copy of the amendment consists of one volume. The review copy consists of one red-jacketed chemistry & manufacturing volume and one separately bound, orange-jacketed bioequivalence volume. The following items are included immediately following the NDA Form 356h:

-Field Copy Certification

We look forward to your early response. If you have any questions or comments regarding this amendment, please contact the undersigned, or as an alternate, Ms. Fran Hutchins, Plant Manager, at Tel. (704) 596-0516.

Sincerely,
VINTAGE PHARMACEUTICALS, INC.

CJ Nascone

Christopher J. Nascone
Regulatory Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
AUG 21 2000
OGD

3241 Woodpark Blvd.
Charlotte, NC 28206

Vintage
Pharmaceuticals, Inc.

(704) 596-0516

March 28, 2000

NDA ORIG AMENDMENT
N/AC

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

Re: ANDA# 40-349
Sulfasalazine Tablets, USP
500 mg
Major Amendment

In accordance with Section 505(j) of the FD&C Act, as amended, and 21 CFR Part 314.94, we are submitting an amendment to the original Abbreviated New Drug Application for:

Sulfasalazine Tablets, USP
500 mg

This amendment is in response to a major deficiency letter dated March 16, 2000.

The archival copy of the amendment consists of one volume. The review copy consists of one red-jacketed chemistry & manufacturing volume and one separately bound, orange-jacketed bioequivalence volume. The following items are included immediately following the NDA Form 356h:

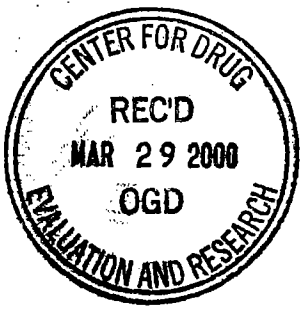
-Field Copy Certification

We look forward to your early response. If you have any questions or comments regarding this amendment, please contact the undersigned, or as an alternate, Ms. Fran Hutchins, Plant Manager, at Tel. (704) 596-0516.

Sincerely,
VINTAGE PHARMACEUTICALS, INC.

C J Nascone

Christopher J. Nascone
Regulatory Affairs



3241 Woodpark Blvd.
Charlotte, NC 28206

Vintage Pharmaceuticals, Inc.

(704) 596-0516

Converted to minor after 30 day extension to respond to FAX def. Notified pls 2/24/00

NDA ORIG AMEND

February 16, 2000

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

Re: ANDA# 40-349
Sulfasalazine Tablets, USP
500 mg
Minor Amendment

In accordance with Section 505(j) of the FD&C Act, as amended, and 21 CFR Part 314.94, we are submitting an amendment to the original Abbreviated New Drug Application for:

Sulfasalazine Tablets, USP
500 mg

This amendment is in response to a fax request dated December 10, 1999.

The archival copy of the amendment consists of one volume. The review copy consists of one red-jacketed chemistry & manufacturing volume and one separately bound, orange-jacketed bioequivalence volume. The following items are included immediately following the NDA Form 356h:

-Field Copy Certification

We look forward to your early response. If you have any questions or comments regarding this amendment, please contact the undersigned, or as an alternate, Ms. Fran Hutchins, Plant Manager, at Tel. (704) 596-0516.

Sincerely,
VINTAGE PHARMACEUTICALS, INC.

CJNascone

Christopher J. Nascone
Regulatory Affairs

CENTER FOR DRUG
RECD
FEB 18 2000
EVALUATION

3241 Woodpark Blvd.
Charlotte, NC 28206

Vintage
Pharmaceuticals, Inc.

(704) 596-0516

February 9, 1999

NDA ONE AMENDMENT

AB

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

RE: Sulfasalazine Tablets 500 mg
ANDA #40-349
Bioequivalence Telephone Amendment

Dear Sir:

As per our telephone conversations of February 2 and February 5, 1999, please find enclosed the following information:

- A copy of ———'s SOP on sample collection. A copy of the processing instructions used in the study and a copy of ——— SOP/Method Report for ———

- The duration of sample storage for both studies is documented in the reports and enclosed are copies of the relevant pages with the sections highlighted. For study 9727014 Period I started on 10/18/97 and the sample analysis completed on 11/23/97. For study 9727022, Period I started on 1/31/98 and sample analysis was completed on 2/27/98.

- Long term stability data that more than covers the maximum duration of the drug substance is provided in the report. Again I have enclosed a copy of the relevant page. You will note that stability samples were prepared on 10/10/97 and wre analyzed on 11/25/97. This exceeds the duration of either study and demonstrated appropriate stability.

If you have any questions or comments regarding this application, please contact the undersigned, or as an alternate, Mr. John Dambrauskas, General Manager, at Tel. (704) 596-0516.

Sincerely,
VINTAGE PHARMACEUTICALS, INC.

RCldr

Rebecca Childers
Manager, Regulatory Affairs

RECEIVED

FEB 11 1999

GENERIC DRUGS

ANDA 40-349

DEC 29 1998

Vintage Pharmaceuticals, Inc.
Attention: Rebecca Childers
3241 Woodpark Blvd.
Charlotte, NC 28206

Dear Madam:

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

Reference is made to the telephone conversation dated December 14, 1998 and your correspondence dated December 14, 1998.

NAME OF DRUG: Sulfasalazine Tablets USP, 500 mg

DATE OF APPLICATION: November 30, 1998

DATE (RECEIVED) ACCEPTABLE FOR FILING: December 2, 1998

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 ANDA number shown above.

Should you have questions concerning this application, contact:

Kassandra Sherrod
Project Manager
(301) 827-5849

Sincerely yours,

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

3241 Woodpark Blvd.
Charlotte, NC 28206

Vintage
Pharmaceuticals, Inc.

(704) 596-0516

NEW CORRESPONDENCE

December 14, 1998

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

N 40349

NEW CORRESPONDENCE

Dear Sir:

As per our phone conversation this morning, please find enclosed the ' ——— cGMP certification. for the Abbreviated New Drug Application for:

Sulfasalazine Tablets, USP
500mg

We look forward to your early response. If you have any questions or comments regarding this application, please contact the undersigned, or as an alternate, Mr. John Dambrauskas, General Manager, at Tel. (704) 596-0516.

Sincerely,
VINTAGE PHARMACEUTICALS, INC.

RCHilders

Rebecca Childers
Manager, Regulatory Affairs

RECEIVED
DEC 15 1998
GENERIC DRUGS

3241 Woodpark Blvd.
rlotte, NC 28206

Vintage Pharmaceuticals, Inc.

FAX #:301-594-1174

(704) 596-0516

DATE: 12/14/98

TO: GREG DAVIS

NEW CORRESP
NC

COMPANY: FDA/OGD

FROM: BECKY CHILDERS

DEPARTMENT: REGULATORY AFFAIRS

Telephone: (704) 596-0516 Fax (704) 598-6237

NUMBER OF PAGES INCLUDING COVER PAGE: 5/6

NEW CORRESPONDENCE

3241 Woodpark Blvd.
Charlotte, NC 28206

Vintage
Pharmaceuticals, Inc.

(704) 596-0516

June 23, 1999

NDA ORIG AMENDMENT
N/Ac

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

RE: Sulfasalazine 500 mg Tablets
ANDA 40-349
Major Deficiency

In response to your June 15,1999 major deficiency letter, Vintage offers the following responses:

OBSERVATION #1 Please include an amount of [redacted] in your Components and Composition statement. If most of the [redacted] is acceptable to record an amount as negligible.

RESPONSE #1 Attachment I Components and Composition Statement.

OBSERVATION #2 Also, the USP designation should be used in your Components and Composition statement for [redacted]

RESPONSE #2 Attachment I Components and Composition Statement.

OBSERVATION #3 Please be advised that the application cannot be approved until deficiencies regarding DMF # [redacted] have been addressed satisfactorily by the holder.

OBSERVATION #4 Since Sulfasalazine is practically insoluble in water, which is the [redacted] solution used, and the DMF holder has a Particle size specification, we recommend that you establish reasonable Particle size and Bulk density specifications in your testing for Sulfasalazine, USP based on the exhibit lot, and include the limits in a revised Certificate of Analysis.

RESPONSE #4 Attachment II- revised drug substance specifications.

OBSERVATION #5 In accordance with 21CFR, you are requested to provide your own in-house Certificates of Analysis which include all compendial testing requirements of USP 23. If you intend to perform periodic testing, this may only be implemented after the vendor is validated. The protocol for vendor validation must be acceptable to the FDA district.

RESPONSE #5 Each active is fully tested upon receipt. Each inactive will have identification testing performed on each lot received once the vendor is validated. Attachment III-Raw material vendor validation protocol.

OBSERVATION #6 The raw material specification for Microcrystalline Cellulose do not appear to be in full accordance with USP 23. See Supp. 9.

RESPONSE #6 Attachment IV-Microcrystalline Cellulose specification.

OBSERVATION #7 [redacted]

concise equipment description. Please clarify and revise.

RESPONSE #7 Attachments-Batch Production Record.

OBSERVATION #8 The "[redacted]" is also an insufficient description. The [redacted] type, manufacturer and capacity should be specified with [redacted]

RESPONSE #8 Attachment V-Batch Production Record.

OBSERVATION #9 [redacted]

RESPONSE #9 Attachment V-Batch Production Record.

OBSERVATION #10 [redacted]

RESPONSE #10 The step has been deleted, more solution should not be required.
Attachment V-Batch Production Record.

OBSERVATION #11 [redacted]

specification listed in the batch records. This should be included.

RESPONSE #11 Attachment V-Batch Production Record.

OBSERVATION #12 [redacted]

RESPONSE #12 [redacted]

OBSERVATION #13

[redacted]

RESPONSE #13

OBSERVATION #14

RESPONSE #14

OBSERVATION #15 We also recommend that you establish an upper limit for your release [redacted] specification.

RESPONSE #15 Attachment VI-Lab Procedure
Attachment VII-Finished Product Specification
Quality Control Report
Certificate of Analysis

OBSERVATION #16 Based on the data provided for batch #097066, we also request that you lower your Individual Impurities specification levels on release.

RESPONSE #16 Attachment VII-Finished Product Specifications
Quality Control Report
Certificate of Analysis
Attachment VI-Lab Procedure

OBSERVATION #17 Please provide information concerning the source and purity factor of your impurity reference standards used in the methods validation.

RESPONSE #17 USP reference standard was used for sulfasalazine.
New line impurity "x" lot # 2228:1727456 had an estimated purity of [redacted]
Impurity "y" lot # 23:220224-5 had an estimated purity of [redacted]
Impurities "x" and "y" were supplied by [redacted]
[redacted] lot # 176-120B had a purity of [redacted]

OBSERVATION #18 Although the HOW SUPPLIED section of the labeling states that the product is scored, the Description specification at release does not include this in the description of the tablet. The COA and the finished product specification

RESPONSE #18 Attachment VII-Finished Product Specifications
Quality Control Report
Certificates of Analysis
Attachment VI-Lab Procedure

OBSERVATION #19 [redacted]

RESPONSE #19 [redacted]

Attachment V-Batch Production Record.

OBSERVATION #20 [redacted]

RESPONSE #20

OBSERVATION #21

RESPONSE #21 The in-process [redacted] has been revised and is included in the batch production record.
Attachment V-batch Production Record.
Attachment IX-In-process specification.

OBSERVATION #22 We also recommend that you establish an upper limit to your ' [redacted] specification on stability.

RESPONSE #22 Attachment VIII-stability Protocols.

OBSERVATION #23 We also request that you tighten your impurities specifications on stability also. The stability data provided do not justify the limits you propose.

RESPONSE #23 Attachment VIII- Stability Protocols

OBSERVATION #24 In accordance with FDA Guidelines, we also recommend that you include a [redacted] specification on release and during stability for the tablets.

RESPONSE #24 Attachment VII-Finished Product Specifications
Quality Control Reports
Certificates of Analysis
Attachment VIII-Stability Protocols

This concludes our response to the deficiency. If further information is needed please do not hesitate to call Rebecca Childers at (704) 596-0516 or John Schultz at (256) 859-2222.

Sincerely,

Rebecca Childers
Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

3241 Woodpark Blvd.
Charlotte, NC 28206

Vintage
Pharmaceuticals, Inc.

(704) 596-0516

505(j)(2)(A) OK
12/15/98
Gregory S. Dr.

November 30, 1998

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

Dear Sir:

In accordance with Section 505(j) of the FD&C Act, as amended, and 21 CFR Part 314.94, we are submitting an original Abbreviated New Drug Application for:

Sulfasalazine Tablets, USP
500mg

In-vivo and in-vitro bioequivalence studies are included in section VI.

The archival copy of the ANDA consists of five volumes. The review copy consists of two red-jacketed chemistry & manufacturing volumes and four separately bound, orange-jacketed bioequivalence volumes. All volumes contain a complete Table of Contents. The following items are included immediately following the NDA Form 356h:

-Prescription Status Statement
-Debarment/Conviction Certification
-Field Copy Certification

We look forward to your early response. If you have any questions or comments regarding this application, please contact the undersigned, or as an alternate, Mr. John Dambrauskas, General Manager, at Tel. (704) 596-0516.

Sincerely,
VINTAGE PHARMACEUTICALS, INC.

Rebecca Childers
Manager, Regulatory Affairs