CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

75-339

Generic Name: Sulfasalazine Delayed-release Tablets, USP

Sponsor: Vintage Pharmaceuticals, Inc.

Approval Date: January 11, 2002

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-339

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-339

APPROVAL LETTER

ANDA 75-339

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 February 20, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Sulfasalazine Delayed-release 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 Delayed-release Tablets USP, 500 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Azulfidine® EN-tabs, 500 mg of Pharmacia & Upjohn Co.).

Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application. The "interim" dissolution specifications are as follows:

> The dissolution testing should be conducted in 900 mL of 0.1N HCl at 37°C using USP 24 Apparatus 1 (basket) at 100 rpm for 2 hours followed by dissolution in 900 mL of phosphate buffer pH 7.5 for 60 minutes. The test product should meet the following interim specifications:
>
> > Not more than ——(Q) of the labeled amount of the dosage form is dissolved in 2 hours (acid stage); and not less than ——(Q) of the labeled amount of the drug in the dosage form is dissolved in 60 minutes (buffer stage).

The "interim" dissolution test(s) and tolerances should be finalized by submitting dissolution data for the first three production size batches. Data should be submitted as a Special Supplement - Changes Being Effected when there are no revisions to the "interim" specifications or when the final specifications are tighter than the "interim" specifications. In all other instances, the information should be submitted in the form of a Prior Approval Supplement.

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 which 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,

/S/ 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:

75-339

APPROVED FINAL LABELING

Sulfasalazine Delayed-release Tablets, USP

Rx only

APPROVED

JAN 1 1 2002

DESCRIPTION

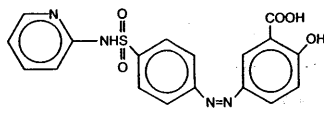
Sulfasalazine Delayed-release Tablets, USP, 500 mg are formulated in a delayed release tablet (enteric-coated) for oral administration.

Sulfasalazine Delayed-release Tablets, USP, 500 mg are film coated with cellulose acetate phthalate to retard disintegration of the tablet in the stomach and reduce potential irritation of the gastric mucosa.

Therapeutic Classification: Anti-inflammatory agent and/or immunomodulatory agent.

Chemical Designation: 5-([p-(2-pyridylsulfamoyl)phenyl]azo) salicylic acid.

Chemical Structure:



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

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. The relative contribution of the parent drug and the major metabolites in rheumatoid arthritis is unknown.

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 hrs. 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 hrs, 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.

Pediatric: Small studies have been reported in the literature in children down to the age of 4 years with ulcerative colitis and inflammatory bowel disease. To date, comparative pharmacokinetic trials have not been conducted to determine whether or not significant pharmacokinetic differences exist between children with juvenile rheumatoid arthritis and adults with rheumatoid arthritis. In these populations, relative to adults, the pharmacokinetics of SSZ and SP correlated poorly with either age or dose.

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 hrs vs. 10.4 hrs) 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 Delayed-release Tablets, USP, 500 mg are 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; and
c) in the treatment of patients with rheumatoid arthritis who have responded inadequately to salicylates or other nonsteroidal anti-inflammatory drugs (e.g., an insufficient therapeutic response to, or intolerance of, an adequate trial of full doses of one or more nonsteroidal anti-inflammatory drugs).

Sulfasalazine Delayed-release Tablets, USP, 500 mg is particularly indicated in patients with ulcerative colitis who cannot take uncoated sulfasalazine tablets because of gastrointestinal intolerance, and in whom there is evidence that this intolerance is not primarily the result of high blood levels of sulfapyridine and its metabolites, e.g., patients experiencing nausea and vomiting with the first few doses of the drug, or patients in whom a reduction in dosage does not alleviate the adverse gastrointestinal effects.

In patients with rheumatoid arthritis, rest and physiotherapy as indicated should be continued. Unlike anti-inflammatory drugs, Sulfasalazine Delayed-release Tablets, USP, 500 mg does not produce an immediate response. Concurrent treatment with analgesics and/or nonsteroidal anti-inflammatory drugs is recommended at least until the effect of Sulfasalazine Delayed-release Tablets, USP, 500 mg is apparent.

Manufactured by
VINTAGE PHARMACEUTICALS, INC.
Charlotte, NC 28206

IN-160
Rev 3/01
R9

8. Korelitz B, et al. Desensitization to sulfasalazine in allergic patients with IBD: an important therapeutic modality. Gastroenterology 1991;30:413-417.
1982;82:1104.
9. Holdworth CG. Sulphasalazine desensitization. Br Med J 1981; 282:110.
10. Taffet SL, Das KM. Desensitization of patients with inflammatory bowel disease to sulfasalazine. Am J Med 1982; 73:520-4.

ADVERSE REACTIONS

The most common adverse reactions associated with sulfasalazine in ulcerative colitis 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 pruritus, urticaria, rash, fever, Heinz body anemia, hemolytic anemia and cyanosis, which may occur at a frequency of 1 in 30 patients or less. Experience suggests that with a daily dose of 4 g or more, or total serum sulfapyridine levels above 50 µg/mL, the incidence of adverse reactions tends to increase.

Similar adverse reactions are associated with sulfasalazine use in adult rheumatoid arthritis, although there was a greater incidence of some reactions. In rheumatoid arthritis studies, the following common adverse reactions were noted: nausea (19%), dyspepsia (13%), rash (13%), headache (9%), abdominal pain (8%), vomiting (8%), fever (5%), dizziness (4%), stomatitis (4%), pruritis (4%), abnormal liver function tests (4%), leukopenia (3%), and thrombocytopenia (1%). One report[7] showed a 10% rate of immunoglobulin suppression, which was slowly reversible and rarely accompanied by clinical findings.

In general, the adverse reactions in juvenile rheumatoid arthritis patients are similar to those seen in patients with adult rheumatoid arthritis except for a high frequency of serum sickness-like syndrome in systemic-course juvenile rheumatoid arthritis (see PRECAUTIONS, Pediatric Use). One clinical trial showed an approximate 10% rate of immunoglobulin suppression.[1]

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 Delayed-release Tablets, USP, 500 mg is administered.

Less common or rare adverse reactions include:

Blood dyscrasias: aplastic anemia, agranulocytosis, megaloblastic (macrocytic) anemia, purpura, 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 variioliformis 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, diarrhea, 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, urinary tract infections, 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 is directly related to the total serum sulfapyridine concentration. Symptoms of overdosage may include nausea, vomiting, gastric distress and abdominal pains. In more advanced cases, central nervous system 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 LD_{50} in laboratory animals such as mice, since the highest oral daily dose of sulfasalazine which can be given (12 g/kg) is not lethal. Doses of regular sulfasalazine tablets 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 by dialysis.

DOSAGE AND ADMINISTRATION

The dosage of Sulfasalazine Delayed-release Tablets, USP, 500 mg should be adjusted to each individual's response and tolerance.

Patients should be instructed to take Sulfasalazine Delayed-release Tablets, USP, 500 mg in evenly divided doses, preferably after meals, and to swallow the tablets whole.

Ulcerative Colitis

Initial Therapy:

Adults: 3 to 4 g daily in evenly divided doses with dosage intervals not exceeding eight hours. It may be advisable to initiate therapy with a lower dosage, e.g., 1 to 2 g daily, to reduce possible gastrointestinal intolerance. If daily doses exceeding 4 g are required to achieve the desired therapeutic effect, the increased risk of toxicity should be kept in mind.

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

Maintenance Therapy:

Adults: 2 g daily.

Children, six years of age and older: 30 mg/kg of body weight in each 24-hour period, divided into 4 doses. The response of acute ulcerative colitis to Sulfasalazine Delayed-release Tablets, USP, 500 mg 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, dosage of Sulfasalazine Delayed-release Tablets, USP, 500 mg should be reduced to a maintenance level. If diarrhea recurs, dosage should be increased to previously effective levels.

Sulfasalazine Delayed-release Tablets, USP, 500 mg is particularly indicated in patients who cannot take uncoated sulfasalazine tablets because of gastrointestinal intolerance (e.g., anorexia, nausea, vomiting, etc.) occur after the first few doses of Sulfasalazine Delayed-release Tablets, USP, 500 mg, they are probably due to increased serum levels of total sulfapyridine, and may be alleviated by halving the daily dose of Sulfasalazine Delayed-release Tablets, USP, 500 mg 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.

Adult Rheumatoid Arthritis:

2 g daily in two evenly divided doses. It is advisable to initiate therapy with a lower dosage of Sulfasalazine Delayed-release Tablets, USP, 500 mg, e.g., 0.5 to 1 g daily, to reduce possible gastrointestinal intolerance. A suggested dosing schedule is given below.

In rheumatoid arthritis, the effect of Sulfasalazine Delayed-release Tablets, USP, 500 mg can be assessed by the degree of improvement in the number and extent of actively inflamed joints. A therapeutic response has been observed as early as 4 weeks after starting treatment with Sulfasalazine Delayed-release Tablets, USP, 500 mg, but treatment for 12 weeks may be required in some patients before clinical benefit is noted. Consideration can be given to increasing the daily dose of Sulfasalazine Delayed-release Tablets, USP, 500 mg to 3 g if the clinical response after 12 weeks is inadequate. Careful monitoring is recommended for doses over 2 g per day.

Suggested Dosing Schedule for Adult Rheumatoid Arthritis:

Week of Treatment	Number of Sulfazsalazine Delayed-release Tablets, USP, 500 mg	
	Morning	Evening
1	-	One
2	One	One
3	One	Two
4	Two	Two

Some patients may be sensitive to treatment with sulfasalazine. Various desensitization-like regimens have been reported to be effective in 34 of 53 patients,[8] 7 of 8 patients,[9] and 19 of 20 patients.[10] 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 Delayed-release Tablets, USP, 500 mg 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.

HOW SUPPLIED

Sulfasalazine Delayed-release Tablets, USP, 500 mg, are oval, gold-colored, convex, coated tablets, debossed "5905" on the top side and "V" on the bottom side. They are available in the following package sizes:

10's, 100's, 300's, 500's and 1000's.

Storage: Store at controlled room temperature 15°-30°C (59°-86°F).

REFERENCES

1. van Rossum MAJ, et al. Sulfasalazine in the treatment of juvenile chronic arthritis: a randomized, double-blind, placebo-controlled, multicenter study. Arth Rheum 1998; 41:808-816.
2. Mogadam M, et al. Pregnancy in inflammatory bowel disease: effect of sulfasalazine and corticosteroids on fetal outcome. Gastroenterology 1981; 80: 726.
3. Kaufman DW, editor. Birth defects and drugs during pregnancy. Littleton, MA: Publishing Sciences Group, Inc., 1977:296-313.
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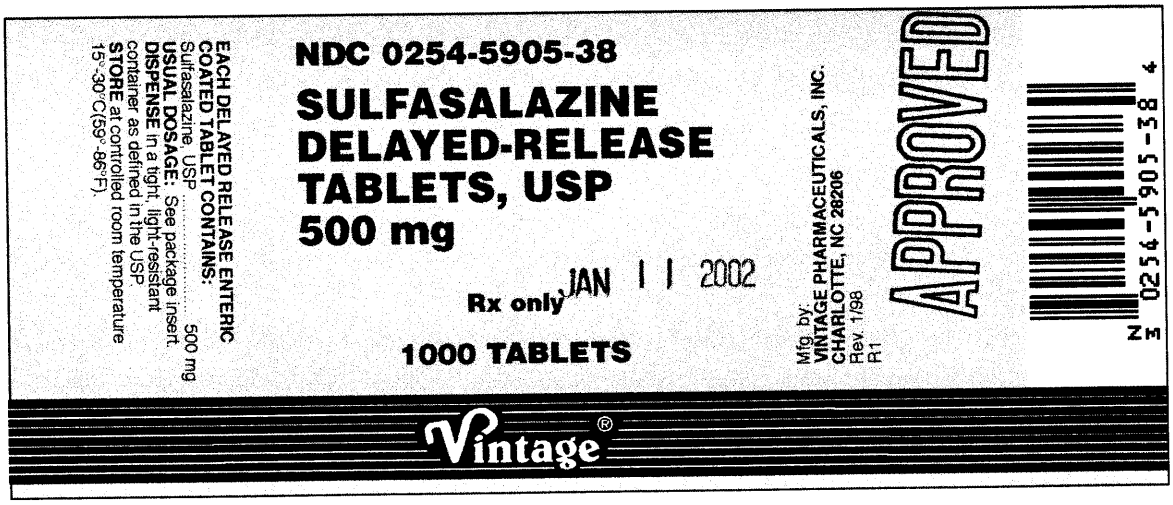
5. Imundo LF, Jacobs JC. Sulfasalazine therapy for juvenile rheumatoid arthritis. J Rheumatol 1996; 23:360-366.
6. Hertzberger-ten Cate R, Cats A. Toxicity of sulfasalazine in systemic juvenile chronic arthritis. Clin Exp Rheumatol 1991;9:85-8.
7. Farr M, et al. Immunodeficiencies associated with sulphasalazine therapy in inflammatory arthritis. British Jnl Rheum



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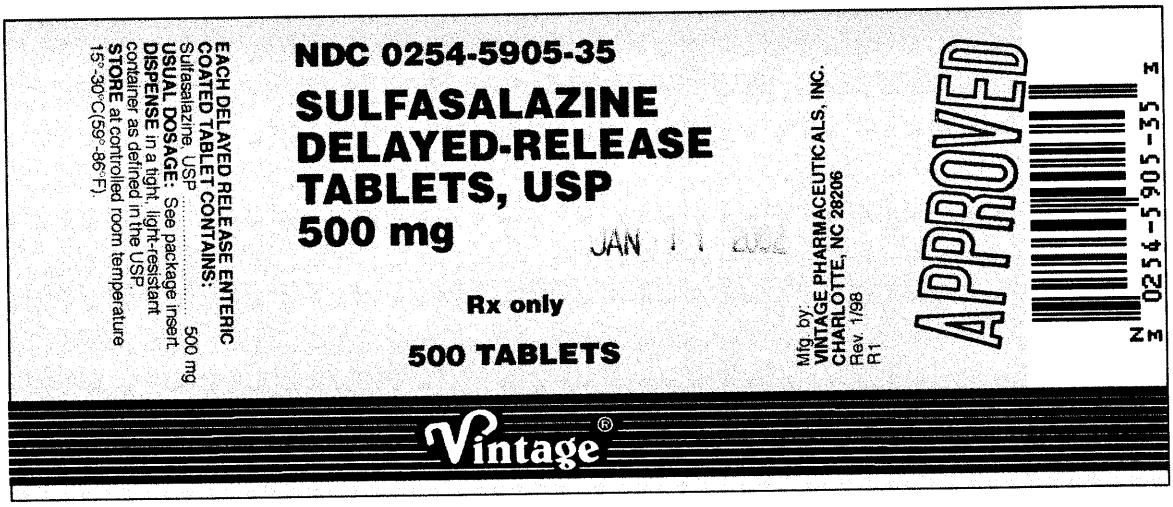

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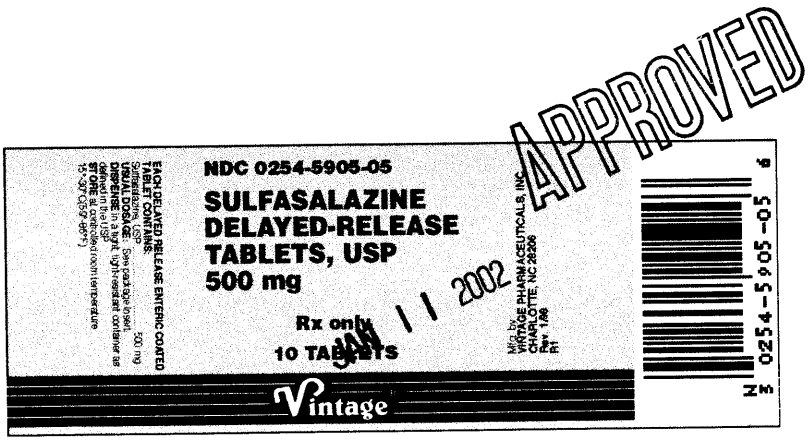

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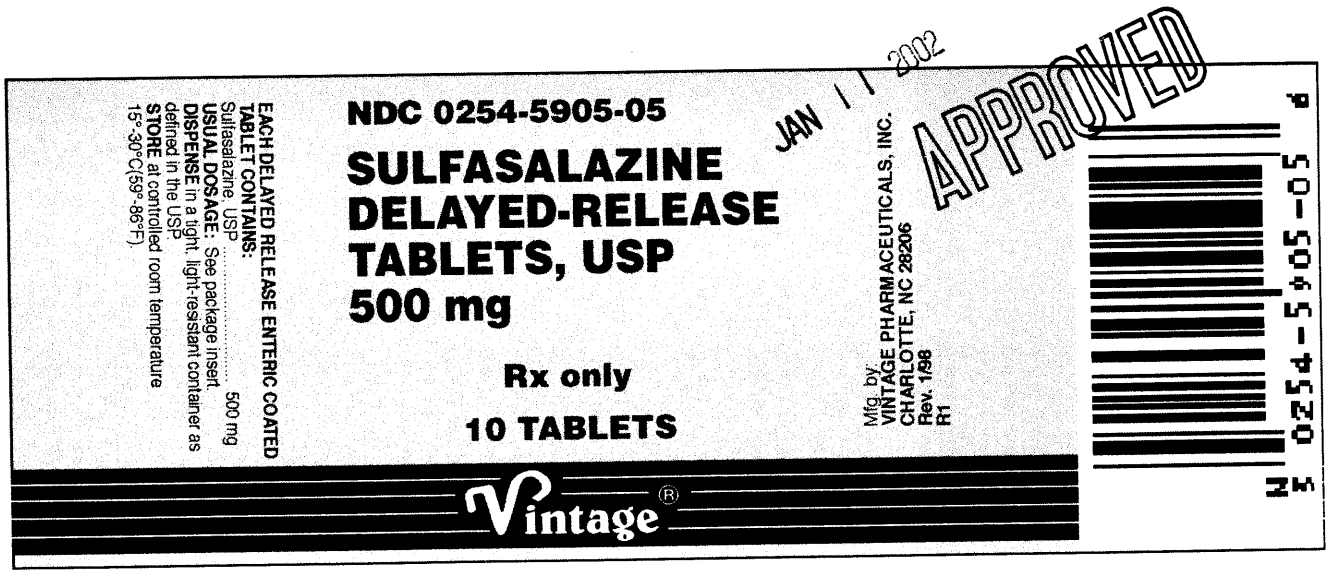

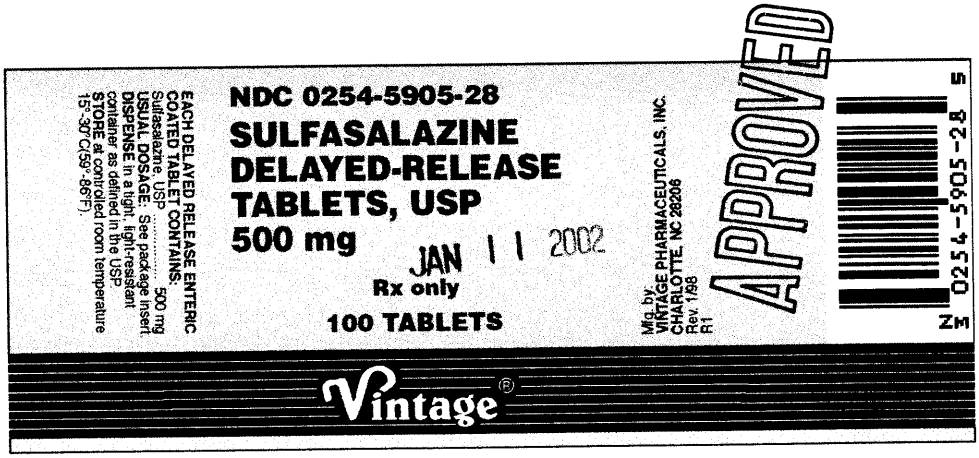

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-339

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 1

2. ANDA # 75-339

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

APPEARS THIS WAY
ON ORIGINAL

4. BASIS OF SUBMISSION
Reference Listed drug product: Azulfidine EN-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
Azulfidine EN[TM]

7. NONPROPRIETARY NAME
Sulfasalazine Tablets

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

APPEARS THIS WAY
ON ORIGINAL

9. AMENDMENTS AND OTHER DATES:
Original submission: 2-20-98
Refuse to File: 4-1-98
Amendment: 2-3-99
Acknowledgement: 3-10-99

10. PHARMACOLOGICAL CATEGORY
Antiulcer

11. Rx or OTC
Rx

APPEARS THIS WAY
ON ORIGINAL

12. RELATED IND/NDA/DMF(s)

[redacted]

13. DOSAGE FORM
Tablets

14. POTENCY
500 mg

15. CHEMICAL NAME AND STRUCTURE
See labeling insert.

APPEARS THIS WAY
ON ORIGINAL

16. RECORDS AND REPORTS
N/A

17. COMMENTS

Chemistry - This application contains chemistry deficiencies. See item #38.

Bioequivalence - Bioequivalence is unacceptable by M. Makary. See deficiency letter dated 4/19/99.

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: 7-13-99

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pages of

trade secret and/or

confidential

commercial

information

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 75-339

APPEARS THIS WAY
ON ORIGINAL

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 EN-Tablets® 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
Azulfidine EN™

7. NONPROPRIETARY NAME
Sulfasalazine Tablets

APPEARS THIS WAY
ON ORIGINAL

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

9. AMENDMENTS AND OTHER DATES:
Original submission: 2-20-98
Refuse to File: 4-1-98
Amendment: 2-3-99
Acknowledgement: 3-10-99
FDA Major deficiency: 7-28-99
Amendment: 8-25-99

10. PHARMACOLOGICAL CATEGORY
Antiulcer

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
Tablets

14. POTENCY
500 mg

15. CHEMICAL NAME AND STRUCTURE

See labeling insert.

APPEARS THIS WAY
ON ORIGINAL

16. RECORDS AND REPORTS
N/A

17. COMMENTS
Chemistry - This application contains chemistry deficiencies. See item #38.
Bioequivalence - Bioequivalence is unacceptable by M. Makary. See deficiency letter dated 9/3/99.
Labeling - Pending
EER - Submitted, awaiting results

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

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

DATE COMPLETED:
2-16-00

20. COMPONENTS AND COMPOSITION

*Revised statement as requested.

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pages of

trade secret and/or

confidential

commercial

information

1. CHEMISTRY REVIEW NO. 3

2. ANDA # 75-339

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

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

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5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
Azulfidine EN™

7. NONPROPRIETARY NAME
Sulfasalazine Tablets

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

9. AMENDMENTS AND OTHER DATES:
Original submission: 2-20-98
Refuse to File: 4-1-98
Amendment: 2-3-99
Acknowledgement: 3-10-99
FDA Major deficiency: 7-28-99
Amendment: 8-25-99
FDA Fax deficiency: 3/7/00
Amendment: 3/10/00

10. PHARMACOLOGICAL CATEGORY
Antiulcer

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
Tablets

14. POTENCY
500 mg

15. CHEMICAL NAME AND STRUCTURE

APPEARS THIS WAY
ON ORIGINAL

See labeling insert.

16. RECORDS AND REPORTS
N/A

17. COMMENTS
Chemistry - This application contains chemistry deficiencies. See item #38.
Bioequivalence - Bioequivalence is unacceptable by M. Makary. See deficiency letter dated 9/3/99.
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:
3-23-00

Redacted 21

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commercial

information

1. CHEMISTRY REVIEW NO. 4

2. ANDA # 75-339

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

APPEARS THIS WAY
ON ORIGINAL

4. BASIS OF SUBMISSION
Reference Listed drug product: Azulfidine EN-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
Azulfidine EN[TM]

7. NONPROPRIETARY NAME
Sulfasalazine Tablets

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

APPEARS THIS WAY
ON ORIGINAL

9. AMENDMENTS AND OTHER DATES:
Original submission: 2-20-98
Refuse to File: 4-1-98
Amendment: 2-3-99
Acknowledgement: 3-10-99
FDA Major deficiency: 7-28-99
Amendment: 8-25-99
FDA Fax deficiency: 3-7-00
Amendment: 3-10-00
FDA Major letter: 3-28-00
Amendment: 3-29-00

10. PHARMACOLOGICAL CATEGORY
Antiulcer

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

[redacted]

13. DOSAGE FORM
Tablets

14. POTENCY
500 mg

15. CHEMICAL NAME AND STRUCTURE

APPEARS THIS WAY
ON ORIGINAL

See labeling insert.

16. RECORDS AND REPORTS
N/A

17. COMMENTS
Chemistry - Some chemistry deficiencies remain.
Bioequivalence - Satisfactory. Bio signoff dated 5/31/00.
Labeling - Satisfactory. See review dated 4/17/00.
EER - Submitted, and found acceptable 10/19/99.

18. CONCLUSIONS AND RECOMMENDATIONS
The application is not approvable. Minor amendment.

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

DATE COMPLETED:
7-25-00

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1. CHEMISTRY REVIEW NO. 5

2. ANDA # 75-339

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

4. BASIS OF SUBMISSION
Reference Listed drug product: Azulfidine EN-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
Azulfidine EN[TM]

7. NONPROPRIETARY NAME
Sulfasalazine Tablets

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

9. AMENDMENTS AND OTHER DATES:
Original submission: 2-20-98
Refuse to File: 4-1-98
Amendment: 2-3-99
Acknowledgement: 3-10-99
FDA Major deficiency: 7-28-99
Amendment: 8-25-99
FDA Fax deficiency: 3-7-00
Amendment: 3-10-00
FDA Major letter: 3-28-00
Amendment: 3-29-00
FDA Minor deficiency: 8-25-00

Amendment: 8-25-00

10. PHARMACOLOGICAL CATEGORY
Antiulcer

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

[redacted]

13. DOSAGE FORM
Tablets

14. POTENCY
500 mg

APPEARS THIS WAY
ON ORIGINAL

15. CHEMICAL NAME AND STRUCTURE

See labeling insert.

16. RECORDS AND REPORTS
N/A

17. COMMENTS
Chemistry - The DMF is deficient. All other chemistry deficiencies have been resolved.
Bioequivalence - Satisfactory. Bio signoff dated 5/31/00.
Labeling - Satisfactory. See review dated 4/17/00.
EER - Submitted, and found acceptable 10/19/99.

18. CONCLUSIONS AND RECOMMENDATIONS
The application is in minor stage until DMF issues resolved.

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

DATE COMPLETED:
9-6-00

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1. CHEMISTRY REVIEW NO. 6

2. ANDA # 75-339

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

4. BASIS OF SUBMISSION
Reference Listed drug product: Azulfidine EN-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
Azulfidine EN[TM]

7. NONPROPRIETARY NAME
Sulfasalazine Tablets

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

9. AMENDMENTS AND OTHER DATES:
Original submission: 2-20-98
Refuse to File: 4-1-98
Amendment: 2-3-99
Acknowledgement: 3-10-99
FDA Major deficiency: 7-28-99
Amendment: 9-3-99
FDA Fax deficiency: 3-7-00
Amendment: 3-10-00
FDA Major letter: 3-28-00
Amendment: 3-29-00
FDA Minor deficiency: 8-25-00

Amendment: 8-25-00
FDA minor Deficiency Letter: 9-15-00
Amendment: 10-11-00

APPEARS THIS WAY ON ORIGINAL

10. PHARMACOLOGICAL CATEGORY
Antiulcer

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
Tablets

14. POTENCY
500 mg

15. CHEMICAL NAME AND STRUCTURE

APPEARS THIS WAY ON ORIGINAL

See labeling insert.

16. RECORDS AND REPORTS
N/A

17. COMMENTS
Chemistry - The DMF is now acceptable. All other chemistry deficiencies have been resolved.
Bioequivalence - Satisfactory. Bio signoff dated 5/31/00.
Labeling - Unsatisfactory as of 1/17/01.
EER - Unacceptable

18. CONCLUSIONS AND RECOMMENDATIONS

The application is now not approvable - minor amendment.

19. REVIEWER: DATE COMPLETED:

Karen A. Bernard, Ph.D. 11-7-00

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1. CHEMISTRY REVIEW NO. 7

2. ANDA # 75-339

APPEARS THIS WAY
ON ORIGINAL

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

4. BASIS OF SUBMISSION
Reference Listed drug product: Azulfidine EN-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
Azulfidine EN[TM]

7. NONPROPRIETARY NAME
Sulfasalazine Delayed Release Tablets

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

APPEARS THIS WAY
ON ORIGINAL

9. AMENDMENTS AND OTHER DATES:
Original submission: 2-20-98
Refuse to File: 4-1-98
Amendment: 2-3-99
Acknowledgement: 3-10-99
FDA Major deficiency: 7-28-99
Amendment: 9-3-99
FDA Fax deficiency: 3-7-00
Amendment: 3-10-00
FDA Major letter: 3-28-00
Amendment: 3-29-00
FDA Minor deficiency: 8-25-00
Amendment: 8-25-00
FDA minor Deficiency Letter: 9-15-00
Amendment: 10-11-00
FDA Minor (labeling): 2-2-01
Amendment: 3-27-01 3/19/01- Minor amendment (BT)
T-Amendment: 5-10-01

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]
DMF [redacted]
DMF [redacted]

13. DOSAGE FORM
Tablets

14. POTENCY
500 mg

APPEARS THIS WAY
ON ORIGINAL

15. CHEMICAL NAME AND STRUCTURE

See labeling insert.

16. RECORDS AND REPORTS
N/A

17. COMMENTS
Chemistry - The DMF is now acceptable. All other chemistry deficiencies have been resolved.
Bioequivalence - Satisfactory. Bio signoff dated 5/31/00.
Labeling - Satisfactory as of 4/6/01.
EER -
Methods-not needed USP drug substance and drug product

18. CONCLUSIONS AND RECOMMENDATIONS
The application is now approvable.

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

DATE COMPLETED:
4-17-01

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-339

BIOEQUIVALENCE REVIEW(S)

(1)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # :75-339 SPONSOR : Vintage Pharmaceuticals, Inc.

DRUG AND DOSAGE FORM : Sulfasalazine Delayed Release Tablets, USP

STRENGTH(S) : 500 mg

TYPES OF STUDIES : Two bioequivalence studies under fasting and nonfasting conditions

CLINICAL STUDY SITE(S) : _____

ANALYTICAL SITE(S) : _____

STUDY SUMMARY : The studies are acceptable

DISSOLUTION : Dissolution testing is acceptable.

DSI INSPECTION STATUS

Inspection needed: YES / (NO)	Inspection status:	Inspection results:
First Generic ✓	Inspection requested: (date)	
New facility _____	Inspection completed: (date)	
For cause _____		
Other _____		

PRIMARY REVIEWER : Moheb H. Makary, Ph.D. BRANCH : III

INITIAL : /S/ _____ DATE : 5/10/01

TEAM LEADER : Barbara M. Davit, Ph.D. BRANCH : III

INITIAL : /S/ _____ DATE : 5/10/00

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : /S/ _____ **DATE :** 5/31/00

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:75-339 APPLICANT: Vintage Pharmaceuticals, Inc.

DRUG PRODUCT: Sulfasalazine Delayed Release Tablets, USP 500 mg

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

We acknowledge that the following dissolution testing has been incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 900 mL of 0.1N HCl at 37°C using USP 24 Apparatus 1 (basket) at 100 rpm for 2 hours followed by dissolution in 900 mL of phosphate buffer pH 7.5 for 60 minutes. The test product should meet the following interim specifications:

> Not more than — (Q) of the labeled amount of the dosage form is dissolved in 2 hours (acid stage); and not less than — (Q) of the labeled amount of the drug in the dosage form is dissolved in 60 minutes (buffer stage).

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,

/S/

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

/S/

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

/S/ 5/10/00

RD INITIALLED BDAVIT /S/

FT INITIALLED BDAVIT

Date: 5/10/00

/S/

Concur: Date: 5/30/00

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Mmakary/4-12-00, 5-10-00, 75339S.3900
cc: ANDA #75-339, original, HFD-658 (Makary), Drug File, Division File.

Sulfasalazine Delayed Release
500 mg Tablets
ANDA #75-339
Reviewer: Moheb H. Makary
W 75339SD.699

Vintage Pharmaceuticals, Inc.
Charlotte, NC
Submission Date:
June 4, 1999

Review of an Amendment

I. Objective:

The firm has replied to the reviewer's comments in the review of the February 3, 1999 submission (bioequivalence study on Sulfasalazine Delayed Release Tablets, 500 mg, and dissolution data).

Comment #1

The firm was asked to submit data to support the long-term stability of sulfapyridine in frozen study samples for the period equal to the time from the first sample collection to the day the last sample was analyzed (40 days).

Firm's Response

The firm submitted the long-term stability of sulfapyridine in frozen study samples for 3.5 months. Assay results demonstrated the stability of sulfapyridine in frozen plasma ($-20^{o}C$) for approximately 3.5 months.

Reply to Firm's Response Comment #1

The firm's response to the comment is acceptable.

Comment #2

The firm was asked to submit a post-prandial bioequivalence study on its Sulfasalazine Delayed-release Tablets, 500 mg. Concentrations of sulfasalazine and sulfapyridine should be determined for the plasma samples collected following administration of the drug. The letter to the firm stated: "The Division of Bioequivalence has recently changed the criteria by which bioequivalence of sulfasalazine drug products is established. Both parent and metabolite should pass point estimate criteria for bioequivalence in a post-prandial bioequivalence study".

Firm's Response

The firm indicated that the sulfasalazine bioequivalence study was performed over 12 months ago. The requirement for the parent and metabolite was not published or in effect at that time. When Vintage was informed on April 1, 1998 that a food study was required, there was no notice or indication of a requirement for the analysis of both metabolites. The firm stated that there is very little sulfasalazine absorbed and the activity is minimal if any compared to the metabolite, sulfapyridine. Because this most recent change in requirements was made effective more than one year after Vintage successfully completed the bioequivalence study according to the then approved guideline, Vintage requests a waiver of requirement to analyze both analytes.

Reply to Firm's Response Comment #2

On April 1, 1998, OGD sent an ANDA Refuse to File letter to Vintage Pharmaceuticals, Inc. In this letter, the firm was asked to provide an *in vivo* bioequivalence study under fed conditions for Sulfasalazine Delayed Release Tablets, 500 mg. The letter did not provide any information regarding a change in criteria by which bioequivalence of sulfasalazine drug products is established. In addition, the firm has indicated that their sulfasalazine bioequivalence study was performed over 12 months ago. On February 3, 1999, the firm submitted an acceptable bioequivalence study on its sulfasalazine Delayed-release Tablets, 500 mg, under fasting conditions. The 90% confidence interval criteria (acceptance range: 80-125%) for log-transformed pharmacokinetic parameters was applied for sulfapyridine to establish bioequivalence under fasting conditions. Therefore, to be consistent with the criteria applied to the fasting study for the firm's post-prandial bioequivalence study on its Sulfasalazine Delayed-release Tablets, 500 mg, only sulfapyridine should be determined in plasma samples collected following administration of the drug. Sulfapyridine should pass point estimate criteria for bioequivalence in the post-prandial bioequivalence study.

The firm's response to the comment is acceptable.

Comment #3

The firm was advised to submit comparative dissolution testing on its Sulfasalazine Delayed-release Tablets, 500 mg, using the following method:

Apparatus: USP XXIII 1 (basket) at 100 rpm
Medium: 900 mL of 0.1N HCl at 37°C for 2 hours (acid stage)
900 mL of phosphate buffer pH 7.5 (buffer stage)
Sampling Times: 30, 60 and 120 minutes (acid stage)
15, 30, 45 and 60 minutes (buffer stage)

Firm's Response

The firm submitted dissolution testing on its Sulfasalazine Delayed-release Tablets, 500 mg, using the above method. The dissolution testing results are shown in Table I.

Reply to Firm's Response Comment #3

The firm's response to the comment is acceptable.

II. Comments:

1. The firm's *in vivo* bioequivalence study conducted on its Sulfasalazine Delayed-release Tablets, 500 mg, under fasting conditions is acceptable.

2. The firm should submit a post-prandial bioequivalence study on its Sulfasalazine Delayed-release Tablets, 500 mg. Only sulfapyridine levels should be determined for the plasma samples collected following administration of the drug.

3. The *in vitro* dissolution testing submitted by the firm on its Sulfasalazine Delayed-release Tablets, 500 mg, is acceptable. It should be noted that the test and the reference products meet the F2 criteria (Table I).

4. In previous applications, bioequivalence of Sulfasalazine drug products was evaluated based on sulfapyridine levels. In future applications, the criteria will be based on sulfasalazine and sulfapyridine levels (please see attachment).

III. Deficiency Comment:

The firm should submit a post-prandial bioequivalence study on its Sulfasalazine Delayed-release Tablets, 500 mg. Only concentration of sulfapyridine levels should be determined for the plasma samples collected following administration of the drug.

IV. Recommendations:

1. The bioequivalence study under fasting conditions conducted by Vintage Pharmaceuticals, Inc., on its Sulfasalazine Delayed-release Tablets, 500 mg, lot #041116D, comparing it to Azulfidine EN-tabs^{R} Tablets, 500 mg, manufactured by Pharmacia & Upjohn, has been found acceptable by the Division of Bioequivalence. The study demonstrates that Vintage's Sulfasalazine Delayed-release Tablets, 500 mg, is bioequivalent to the reference product, Azulfidine EN-tabs^{R} Tablets, 500 mg, manufactured by Pharmacia & Upjohn under fasting conditions.

2. The firm should submit a post-prandial bioequivalence study on its Sulfasalazine Delayed-release Tablets, 500 mg.

3. The dissolution testing conducted by the firm on its Sulfasalazine Delayed-release Tablets, 500 mg, lot #041116D, is acceptable.

4. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of 0.1N HCl at 37°C using USP 23 Apparatus 1 (basket) at 100 rpm for 2 hours followed by dissolution in 900 mL of phosphate buffer pH 7.5 for 60 minutes. The test product should meet the following interim specifications:

> Not more than [redacted] (Q) of the labeled amount of the dosage form is dissolved in 2 hours (acid stage); and not less than [redacted] (Q) of the labeled amount of the drug in the dosage form is dissolved in 60 minutes (buffer stage).

The firm should be informed of the deficiency comment and recommendations

/S/

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

/S/ 8/5/99

RD INITIALLED BDAVIT
FT INITIALLED BDAVIT /S/ _____ Date: 8/9/99

Concur. /S/ Date: 8/10/99
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Mmakary/6-30-99, 7-9-99, 8-9-99, 75339sd.699
cc: ANDA #75-339, original, HFD-658(Makary), Drug File, Division File.

APPEARS THIS WAY
ON ORIGINAL

Sulfasalazine Delayed Release
500 mg Tablets
ANDA #75-339
Reviewer: Moheb H. Makary
W 75339S.300

Vintage Pharmaceuticals, Inc.
Charlotte, NC
Submission Date:
March 30, 2000

Review of an Amendment

I. Objective:

The firm has submitted a bioequivalence study under fasting and nonfasting conditions on its Sulfasalazine Delayed Release (DR) Tablet, 500 mg, comparing the test product to Pharmacia & Upjohn's Azulfidine EN-tabs^{R} Enteric-coated tablets, 500 mg.

II. Background:

The firm has submitted a bioequivalence study on its Sulfasalazine DR Tablet, 500 mg, under fasting and nonfasting conditions as a response to the Agency's letter dated September 3, 1999. In the letter the firm was advised to submit its previously completed post-prandial bioequivalence study on its Sulfasalazine DR Tablets, 500 mg, as the firm described in the amendment dated June 4, 1999. It should also be noted that in the original submission the single dose bioequivalence study under fasting conditions was found acceptable.

The same lot of Sulfasalazine DR Tablet, 500 mg, that was given in the fasting study was also administered in this study.

III. Study #9827005 for Single-Dose, 3-way Crossover Study of Sulfasalazine DR Tablets, 500 mg, Under Fasting and Nonfasting Conditions

Clinical site: [redacted]

Analytical site: [redacted]

Study date: Period I 5/6/98
Period II 5/20/98
Period II 6/3/98

Sample analysis: Sample analysis began on June 18, 1998 and was completed on July 7, 1998.

Subjects:	Seventeen (17) subjects entered and sixteen (16) subjects successfully completed the study. Subject #7 voluntarily withdrew from the study participation for personal reasons after completing Period I.
Selection criteria:	Selection criteria listed in Vol. 4.1, page 0062.
Study design:	Open-label, randomized, 3-way crossover, six-sequence study under fasting and nonfasting conditions.
Dose and treatment:	All subjects completed an overnight fast (at least ten hours) before any of the following drug treatments:
Test Product:	A) 4x500 mg Sulfasalazine Delayed-release Tablets (Vintage), lot #041116D, following a standard breakfast.
	B) 4x500 mg Sulfasalazine Delayed-release Tablets (Vintage), lot #041116D, under fasting conditions.
Reference Product:	C) 4x500 mg Azulfidine EN-tabs^{R} Enteric-coated Tablets (Pharmacia & Upjohn), lot #YB3425A, Exp. 1/2000, following a standard breakfast.
Food and fluid intake:	Subjects on regimens A and C were required to fast overnight until 15 minutes prior to their scheduled dosing times, when they were administered breakfast (1 fried egg, 1 serving of hashed browned potatoes, 1 slice Canadian bacon, 1 buttered English muffin, 1 slice American cheese, 8 ounces of whole milk and 6 ounces of orange juice). Subjects on regimen B were required to fast overnight for 10 hours before dosing and for 4 hours thereafter. Water was restricted from two hours before until two hours after dosing except for water (240 mL) administered with the dose.

Washout period: Two weeks

Assay Methodology

[redacted]

Statistical Methods

[redacted]

IV. In Vivo Results:

All adverse events were mild or moderate. No serious adverse events occurred during the study . The adverse events are summarized in page 0016, Vol 4.1.

The plasma concentrations and pharmacokinetic parameters for sulfapyridine are summarized in Table I.

Table I
Mean Sulfapyridine Plasma Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 4x500 mg Sulfasalazine DR Tablets Under Fasting and Nonfasting Conditions
(N=16)

Time hr	A Vintage Test Product Lot #041116D Nonfasting ug/mL (CV%)	B Vintage Test Product Lot #041116D Fasting ug/mL (CV%)	C Pharmacia&Upjohn Reference Product Lot #YB3425A Nonfasting ug/mL (CV%)
0	0.00	0.00	0.00
1	0.00	0.00	0.00

2	0.00	0.00	0.02 (400)
3	0.00	0.08 (201)	0.05 (400)
4	0.00	0.63 (155)	0.08 (400)
5	0.00	1.81 (101)	0.08 (400)
6	0.02 (400)	3.80 (67.2)	0.08 (400)
8	0.49 (130)	6.00 (55.1)	0.17 (180)
10	1.78 (88.8)	7.50 (49.9)	1.01 (139)
12	3.87 (54.2)	8.68 (50.6)	2.24 (101)
14	5.22 (53.7)	8.29 (40.7)	3.14 (89.1)
16	5.87 (50.1)	8.04 (44.8)	3.40 (81.9)
24	6.01 (65.2)	5.94 (64.4)	4.91 (85.0)
30	5.72 (69.6)	4.04 (89.9)	7.44 (65.5)
36	5.37 (107)	2.87 (107)	6.01 (87.6)
48	2.52 (120)	0.54 (10.4)	2.95 (112)

PK PARAMETER	N	FED TEST TREATMENT A	N	FASTING TEST TREATMENT B	N	FED REF TREATMENT C
AUCT [ug hr/mL]	16	189.8 (63.2)	16	210.1 (59.6)	16	181.2 (56.7)
AUCI [ug hr/mL]	12	238.7 (109.9)	14	248.8 (85.9)	11	222.4 (105.8)
Cmax [ug/mL]	16	8.89 (50.3)	16	9.71 (39.0)	16	9.03 (49.5)
Tmax [hr]	16	22.6 (35.5)	16	14.0 (32.2)	16	25.5 (27.2)
Kel [1/hr]	12	0.0907 (41.2)	14	0.0916 (45.0)	11	0.1009 (41.3)
T1/2 [hr]	12	10.24 (78.7)	14	9.69 (62.8)	11	9.1 (75.1)

	A/C Arithmetic Mean	A/C Geometric Mean
AUC(0-t)	1.05	1.02
AUCinf	1.07	1.02
Cmax	0.98	0.99

1. The sulfapyridine plasma levels peaked at 24 and 30 hours for the test and reference products, respectively, under nonfasting conditions and at 12 hours for the test product under fasting conditions.

2. For Vintage's sulfapyridine, the mean AUC(0-t), AUCinf and Cmax values were 4.7%, 7.3% and 1.6% higher and lower, respectively, than the reference product values under nonfasting conditions. The ratios of the test arithmetic means to the reference arithmetic means are within the acceptable range of

0.8-1.2 for the above parameters. Also, the ratios of the geometric means are within the acceptable 0.8-1.25 range for AUC(0-t), AUCinf and Cmax. The reviewer's calculations are similar to those submitted by the firm.

3. The firm's financial disclosure statements submitted with the bioequivalence section in support of this application did not indicate any conflict of interests between the CRO's investigators and the firm. The reviewer agrees with that conclusion.

V. Recommendations:

1. The bioequivalence studies under fasting and nonfasting conditions conducted by Vintage Pharmaceuticals, Inc., on its Sulfasalazine Delayed-release Tablets, 500 mg, lot #041116D, comparing it to Azulfidine EN-tabs^{R} Tablets, 500 mg, manufactured by Pharmacia & Upjohn, have been found acceptable by the Division of Bioequivalence. The studies demonstrate that Vintage's Sulfasalazine Delayed-release Tablets, 500 mg, is bioequivalent to the reference product, Azulfidine EN-tabs^{R} Tablets, 500 mg, manufactured by Pharmacia & Upjohn under fasting and nonfasting conditions.

2. The dissolution testing conducted by the firm on its Sulfasalazine Delayed-release Tablets, 500 mg, lot #041116D, is acceptable.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of 0.1N HCl at 37°C using USP 24 Apparatus 1 (basket) at 100 rpm for 2 hours followed by dissolution in 900 mL of phosphate buffer pH 7.5 for 60 minutes. The test product should meet the following interim specifications:

> Not more than —— (Q) of the labeled amount of the dosage form is dissolved in 2 hours (acid stage); and not less than —— (Q) of the labeled amount of the drug in the dosage form is dissolved in 60 minutes (buffer stage).

The firm should be informed of the above recommendations.

SULFASALAZINE STUDY NO. 9827005

LEAST-SQUARES MEAN SULFAPYRIDINRE CONCENTRATIONS (N=16)

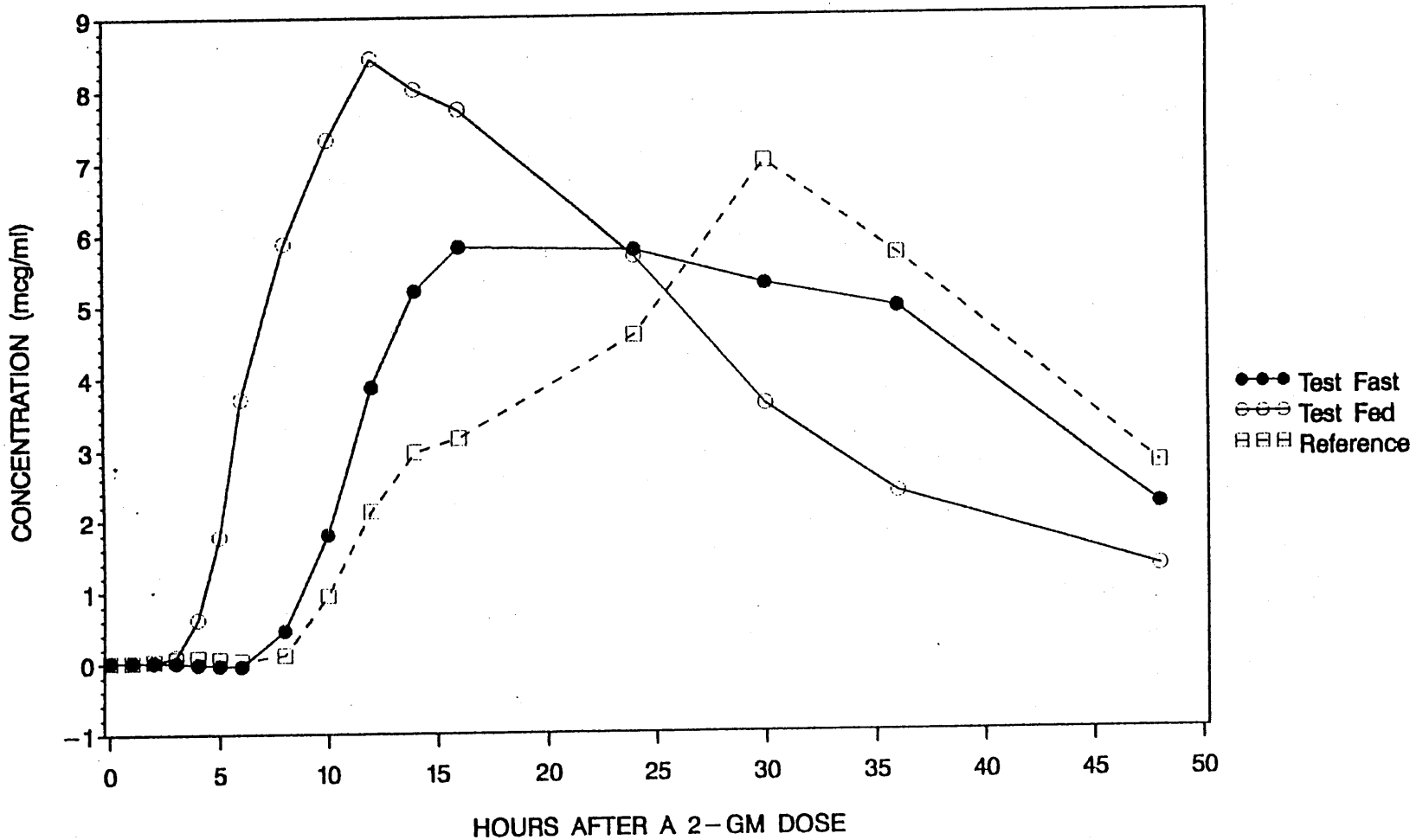

Table I. In Vitro Dissolution Testing

Drug (Generic Name): Sulfasalazine DR Tablets, 500 mg
Dose Strength: 500 mg
ANDA No.: 75-339
Firm: Vintage Pharmaceuticals, Inc.
Submission Date: June 4, 1999
File Name: 75339sd.699

I. Conditions for Dissolution Testing:

USP 23 Basket: X Paddle: RPM: 100
No. Units Tested: 12
Medium: 900 mL of 0.1N HCl for 2 hours (acid stage)
900 mL of phosphate buffer pH 7.5 (buffer stage)
Specifications: NMT — (Q) in 120 minutes (acid stage)
NLT — (Q) in 60 minutes (buffer stage)
Reference Drug: Azulfidine EN-tabs^{R} Tablets, 500 mg
Assay Methodology: —

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # 04116D Strength(mg) 500			Reference Product Lot #YB3425A Strength(mg) 500		
	Mean %	Range	%CV	Mean %	Range	%CV
30	00			00		
60	00			00		
120	00			00		
135	91.1	—	5.7	93.6	—	2.6
150	100.6	—	3.1	101.6	—	2.8
165	101.4	—	2.6	100.4	—	2.0
180	102.4	—	2.5	99.8	—	2.2

Date 6/30/99
USER MHM
n = 4

F2 = 83.08

ANDA # 75-339

Test	Ref	(R-T)2
91.1	93.6	6.25
100.6	101.6	1.00
101.4	100.4	1.00
102.4	99.8	6.76

CC: ANDA #75-339
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

Endorsements: (Draft and Final with Dates)
HFD-658 /Reviewer M. Makary /S/
HFD-658/Bio Team Leader [illegible] Davis /S/ 8/12/99
HFD-617/Project Manage /S/ 8/16/99
HFD-650/Dale Conner

V:\FIRMSNZ\VINTAGE\LTRS&REV\75339sd.699
BIOEQUIVALENCY - DEFICIENCIES Submission Date: June 4, 1999

1. **STUDY AMENDMENT** (STA)

Strengths: 500 mg
Outcome: IC

Outcome Decisions:
IC - Incomplete

APPEARS THIS WAY
ON ORIGINAL

SEP 3 1999

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-339 APPLICANT: Vintage Pharmaceuticals, Inc.

DRUG PRODUCT: Sulfasalazine Delayed Release Tablets, 500 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

Please submit your previously completed post-prandial bioequivalence study on your Sulfasalazine Delayed-release Tablets, 500 mg, as you described in the amendment dated June 4, 1999. Sulfapyridine should pass point estimate criteria for bioequivalence in this previously completed post-prandial bioequivalence study. Please note that, for future applications for Sulfasalazine drug products, the Division of Bioequivalence requests that both sulfasalazine and sulfapyridine meet bioequivalence criteria.

APPEARS THIS WAY
ON ORIGINAL

Sincerely yours,

/S/

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

2.1

APR 19 1999

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-339 APPLICANT: Vintage Pharmaceuticals, Inc.

DRUG PRODUCT: Sulfasalazine Delayed-release 500 mg Tablet

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. Please submit data to support the long-term stability of sulfapyridine in frozen study samples for the period equal to the time from the first sample collection to the day the last sample was analyzed (40 days).

2. Please submit a post-prandial bioequivalence study on your Sulfasalazine Delayed-release Tablets, 500 mg. Concentrations of sulfasalazine and sulfapyridine should be determined for the plasma samples collected following administration of the drug. The Division of Bioequivalence has recently changed the criteria by which bioequivalence of sulfasalazine drug products is established. Both parent and metabolite should pass point estimate criteria for bioequivalence in a post-prandial bioequivalence study.

3. You conducted the dissolution testing using phosphate buffer pH 7.5 (buffer stage) with no prior testing in acid media (acid stage) as recommended by USP for Delayed-release (Enteric-coated) products. You are advised to submit comparative dissolution testing on your Sulfasalazine Delayed-release Tablets, 500 mg using the following method:

Apparatus: USP XXIII 1 (basket) at 100 rpm
Medium: 900 mL of 0.1N HCl at 37°C for 2 hours (acid stage)
900 mL of phosphate buffer pH 7.5 (buffer stage)
Sampling
Times: 30, 60 and 120 minutes (acid stage)
15, 30, 45 and 60 minutes (buffer stage)

Sincerely yours,

/S/

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

Sulfasalazine Delayed Release
500 mg Tablets
ANDA #75-339
Reviewer: Moheb H. Makary
W 75339SD.299

Vintage Pharmaceuticals, Inc.
Charlotte, NC
Submission Date:
February 3, 1999

Review of a Bioequivalence Study and Dissolution Data

I. Objective:

Vintage Pharmaceuticals, Inc., has submitted an *in vivo* bioequivalence study (single-dose fasting) comparing its test product Sulfasalazine 500 mg Delayed-release Tablets to the reference listed product, Pharmacia & Upjohn's Azulfidine EN-tabs^{R} Enteric-coated tablets, 500 mg. The firm also submitted comparative *in vitro* dissolution data.

III. Background

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

Sulfasalazine (SS) is synthesized by diazotization of sulfapyridine (SP) 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 (5-ASA). Following an oral administration of a single 2g of sulfasalazine delayed-release tablets, peak serum concentrations occur within 3-12 hours and average 6 ug/mL. Peak serum sulfapyridine concentrations occur within 12 and 24 hours and average 13 ug/mL. The total recovery of SS and its SP metabolites from the urine of healthy subjects 3 days after the administration of a single 2g dose of Azulfidine EN-tabs^{R} averaged 81%.
The serum concentration of 5-ASA in patients with ulcerative colitis was found to range from 0 to 4 ug/mL, and to exist mainly in the form of free 5-ASA. The urinary recovery of this compound was mostly in the acetylated form.

III. Study# 9727015 For Single-Dose Fasting Bioequivalence Of Vintage's Sulfasalazine Delayed-Release, 500 mg Tablets

Clinical site: [redacted]

Analytical site: [redacted]

Study date:	Group I (subjects 1-16) Period I 9/13/1997 Period II 9/27/97 Group II (subjects 17-26) Period I 9/19/1997 Period II 10/3/97
Sample analysis:	Sample analysis began on October 8, 1997 and was completed on October 21, 1997.
Study design:	A single-dose, randomized, two-treatment, two-period, two-sequence crossover design.
Subjects:	A total of twenty-six (26) healthy adult, male subjects were entered into the study and 25 subjects completed the study.
Selection criteria:	Selection criteria listed in Vol. 1.2, page 0092.
Dose and treatment:	All subjects completed an overnight fast (at least ten hours) before any of the following drug treatments:
Test Product:	a) 4x500 mg Sulfasalazine Delayed-release Tablets (Vintage), lot #041116D, batch size ——— Tablets, Exp. 10/98, potency 99.3%, content uniformity 100.5% (%CV=1.9).
Reference Product:	b) 4x500 mg Azulfidine EN-tabs^{R} Enteric-coated Tablets (Pharmacia & Upjohn), lot #YB3425A, Exp. 1/2000, potency 97.5%, content uniformity 98.2% (%CV=2.1).
Washout period:	Two weeks
Food and fluid intake:	Subjects fasted overnight for at least 10 hours before dosing and for 4 hours thereafter. Water was not permitted for 2 hours before until 2 hours after dosing, but was allowed at all other times. Standard meals were provided at approximately 4 and 9

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Statistical Methods

AUC(0-t), AUCinf, Cmax, Tmax, Ke and T1/2 were calculated from the individual concentration versus time data for sulapyridine. An analysis of variance (ANOVA) was applied to log-transformed and non-transformed bioequivalence parameters to determine any statistically significant ($p<0.05$) differences between the drug formulations. The 90% confidence intervals were calculated for each bioequivalence parameter.

IV. In Vivo Results:

The study was conducted at Novum Inc., during the period of September 13 and October 3, 1997. Twenty-six (26) healthy male subjects were entered into the study and 25 completed the study. Subject #10 did not return for period II due to a personal emergency. All adverse events were mild or moderate. No serious adverse events occurred during the study (Vol 1.2, page 0115).

The plasma concentrations and pharmacokinetic parameters for sulfapyridine are summarized in Table I.

Table I

Mean Sulfapyridine Plasma Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 4x500 mg Sulfasalazine DR Tablets Under Fasting Conditions
(N=25)

Time hr	Vintage Test Product Lot #041116D ug/mL (CV%)	Pharmacia&Upjohn Reference Product Lot #YB3425A ug/mL (CV%)
0	0.00	0.01 (500)
1	0.00	0.00
2	0.00	0.00
3	0.05 (275)	0.03 (378)
4	0.56 (156)	0.24 (286)

5	2.40 (96)	1.55 (105)
6	4.80 (71)	4.36 (66)
8	7.64 (57)	8.00 (45)
10	9.34 (43)	9.90 (36)
12	10.83 (31)	10.66 (31)
14	10.30 (28)	10.86 (32)
16	9.85 (31)	10.48 (34)
24	7.12 (52)	7.39 (51)
30	4.87 (64)	5.03 (62)
36	3.44 (76)	3.52 (72)
48	1.91 (99)	1.93 (90)
72	0.60 (126)	0.62 (116)

Pharmacokinetic Parameters

	Test	Reference	T/R	90% CI
AUC(0-t) (ug.hr/mL)	286.1(46)	295.3(46)	0.99	92.4-103.5
AUCinf (ug.hr/mL)	302.7(50)	306.9(50)	0.99	94.9-104.7
Cmax (ug/mL)	12.1(27)	12.3(24)	0.98	92.1-105.0
Tmax (hr)	12.7	12.96		
Kel(1/hr)	0.08	0.08		
t1/2 (hr)	10.81	10.92		

	Mean SD	Mean SD	RMSE
LnAUC (0-t)	5.54(0.51)	5.57 (0.53)	0.12
LnAUCinf	5.58(0.54)	5.59 (0.56)	0.10
LnCmax	2.46(2.27)	2.47 (0.26)	0.14

1. For Vintage's sulfapyridine, the mean AUC(0-t), AUCinf and Cmax values were 3.1%, 1.4% and 1.6% lower, respectively, than those for the reference product values. The 90% confidence intervals are within the acceptable range of 80-125% for log-transformed AUC(0-t), AUCinf and Cmax.

2. The sulfapyridine plasma levels peaked at 12 and 14 hours for the test and the reference products, respectively, following the administration of sulfasalazine dosing under fasting conditions.

3. Additional analysis of variance was performed by the reviewer, after employing the following model

Y = GRP SEQ SUBJ(SEQ*GRP) PER(GRP) TRT GRP*TRT;

Since the group*treatment effect was not significant, it was dropped from the subsequent ANOVA model used for data analysis.

The following 90% confidence intervals for LnAUC(0-t), LnAUCinf and LnCmax were obtained:

Sulfapyridine

LnAUC(0-t)	91.9-103.2%
LnAUCinf	94.4-104.0%
LnCmax	91.3-104.6%

The 90% confidence intervals for the above pharmacokinetics parameters calculated using the above model remained within the acceptable range of 80-125%.

V. Formulation:

The formulation for sulfasalazine DR, 500 mg tablets is shown in Table II.

VI. In Vitro Dissolution Testing:

Method:	USP 23 apparatus I at 100 rpm
Medium:	900 mL of phosphate buffer, pH 7.5
Number of Tablets	12
Test product:	Vintage's Sulfasalazine DR Tablets 500 mg, lot #041116
Reference product:	Pharmacia & Upjohn's Azulfidine EN-tabs^{R} Tablets, 500 mg, lot #YB3425A

Dissolution testing results are shown in Table III.

VII. Comments:

1. The firm's *in vivo* bioequivalence study conducted on its Sulfasalazine Delayed-release Tablets, 500 mg, under fasting conditions is acceptable. The 90% confidence intervals for LnAUC(0-t), LnAUCinf and LnCmax are within the acceptable range of 80-125% under fasting conditions for sulfapyridine.

2. The firm should submit a post-prandial bioequivalence study on its Sulfasalazine Delayed-release Tablets, 500 mg. Concentrations of sulfasalazine and sulfapyridine should be determined for the plasma samples collected following administration of the drug.

3. The firm conducted its dissolution testing using phosphate buffer pH 7.5 (buffer stage) with no prior testing in acid media (acid stage) as recommended by USP for Delayed-release (Enteric-coated) products. Therefore, the dissolution testing is unacceptable.

VIII. Deficiency Comments:

1. The firm should submit data to support the long-term stability of sulfapyridine in frozen study samples for the period equal to the time from the first sample collection to the day the last sample was analyzed (40 days).

2. The firm should submit a post-prandial bioequivalence study on its Sulfasalazine Delayed-release Tablets, 500 mg. Concentrations of sulfasalazine and sulfapyridine should be determined for the plasma samples collected following administration of the drug. The parent compound sulfasalazine is quantifiable and has been used to establish bioequivalence between the innovator's sulfasalazine formulations (NDA #N07073).

3. The firm conducted its dissolution testing using phosphate buffer pH 7.5 (buffer stage) with no prior testing in acid media (acid stage) as recommended by USP for Delayed-release (Enteric-coated) products.

The firm should submit comparative dissolution testing on its Sulfasalazine Delayed-release Tablets, 500 mg using the following method:

Apparatus: USP XXIII 1 (basket) at 100 rpm
Medium: 900 mL of 0.1N HCl at 37°C for 2 hours (acid stage)
900 mL of phosphate buffer pH 7.5 (buffer stage)
Sampling Times: 30, 60 and 120 minutes (acid stage)
15, 30, 45 and 60 minutes (buffer stage)

XI. Recommendations:

1. The bioequivalence study under fasting conditions conducted by Vintage Pharmaceuticals, Inc., on its Sulfasalazine Delayed-release 500 mg Tablet, lot #041116D, comparing it to Azulfidine EN-tabs^{R} 500 mg Tablet manufactured by Pharmacia & Upjohn, has been found incomplete by the Division of Bioequivalence for the reasons given in deficiency comments 1.

2. Because this drug product is a delayed-release formulation the firm should submit a post-prandial bioequivalence study.

3. The dissolution testing conducted by Vintage Pharmaceuticals, Inc., on its Sulfasalazine Delayed-release 500 mg Tablets, lot #041116D comparing, it with the respective strength of Pharmacia & Upjohn's to Azulfidine EN-tabs^{R} 500 mg Tablet is unacceptable for the reason given in deficiency comment #3.

The firm should be informed of the deficiency comments and recommendations.

/S/

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

/S/ 3/30/99

RD INITIALLED BDAVIT
FT INITIALLED BDAVIT /S/ Date: 3/30/99

Concur: /S/ Date: 3/31/99
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Mmakary/3-26-99, 75339SD.299
cc: ANDA #75-339, original, HFD-658(Makary), Drug File, Division File.

APPEARS THIS WAY ON ORIGINAL

SULFASALAZINE STUDY NO. 9727015

LEAST – SQUARES MEAN SULFAPYRIDINE PLASMA CONCENTRATIONS (N = 25)

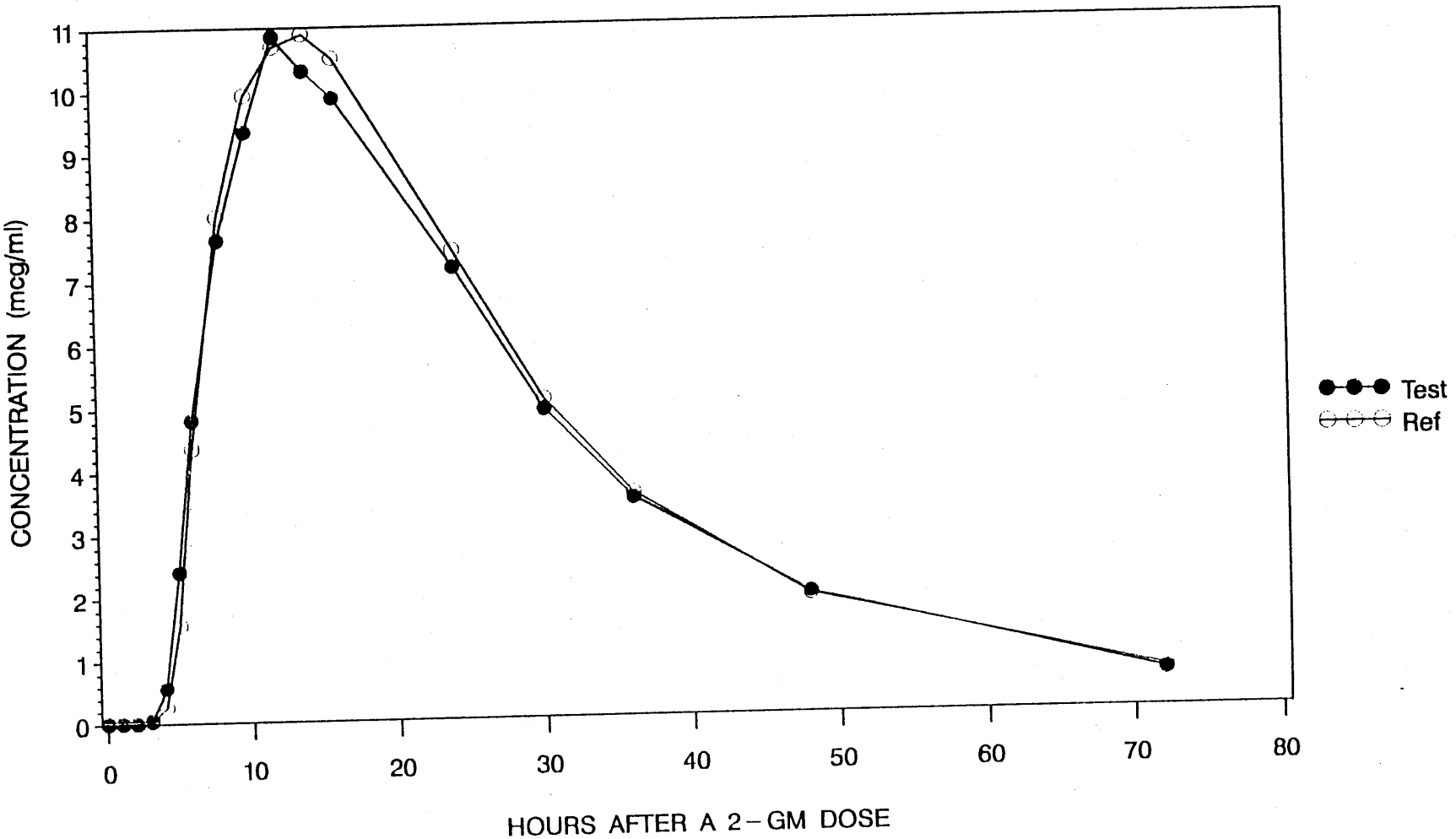

Table II

VINTAGE PHARMACEUTICALS, INC.
Sulfasalazine DR, EC Tablets
500 mg

COMPONENTS AND COMPOSITION STATEMENT

Sulfasalazine Delayed Release, Enteric Coated Tablets, USP
500 mg

Ingredient	per tablet	Quantity per batch
Sulfasalazine, USP	[redacted]	[redacted]
	[redacted]	[redacted]
Enteric Coating		
Cellulose Acetate Phthalate	[redacted]	[redacted]
	[redacted]	[redacted]
Total Weight	822.63 mg	822.630 kg

[redacted] 2-17-98
Approved - Manufacturing Date

[redacted] 2/17/98
Approved - Regulatory Affairs Date

Table III. In Vitro Dissolution Testing

Drug (Generic Name): Sulfasalazine Delayed-release 500 mg Tablets
Dose Strength: 500 mg
ANDA No.: 75-339 Firm: Vintage Pharmaceuticals, Inc.
Submission Date: February 3, 1999
File Name: 75339SD.299

I. Conditions for Dissolution Testing:

USP 23 Basket: X Paddle: RPM: 100
No. Units Tested: 12
Medium: 900 mL of phosphate buffer pH 7.5
Specifications: NLT — (Q) in 60 minutes
Reference Drug: to Azulfidine EN-tabs[R] 500 mg Tablet
Assay Methodology: —

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # 041116 Strength(mg) 500			Reference Product Lot # YB3425A Strength(mg) 500		
	Mean %	Range	%CV	Mean %	Range	%CV
15	7.8	—	29.5	90.1	—	12.9
30	93.4	—	4.0	99.4	—	1.5
45	10.20	—	4.0	99.8	—	1.6
60	102.2	—	3.8	99.8	—	1.4

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75-339 APPLICANT: Vintage Pharmaceuticals, Inc.

DRUG PRODUCT: Sulfasalazine Delayed-release 500 mg Tablet

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. Please submit data to support the long-term stability of sulfapyridine in frozen study samples for the period equal to the time from the first sample collection to the day the last sample was analyzed (40 days).

2. Please submit a post-prandial bioequivalence study on your Sulfasalazine Delayed-release Tablets, 500 mg. Concentrations of sulfasalazine and sulfapyridine should be determined for the plasma samples collected following administration of the drug. The Division of Bioequivalence has recently changed the criteria by which bioequivalence of sulfasalazine drug products is established. Both parent and metabolite should pass point estimate criteria for bioequivalence in a post-prandial bioequivalence study.

3. You conducted the dissolution testing using phosphate buffer pH 7.5 (buffer stage) with no prior testing in acid media (acid stage) as recommended by USP for Delayed-release (Enteric-coated) products. You are advised to submit comparative dissolution testing on your Sulfasalazine Delayed-release Tablets, 500 mg using the following method:

Apparatus: USP XXIII 1 (basket) at 100 rpm
Medium: 900 mL of 0.1N HCl at 37°C for 2 hours (acid stage)
900 mL of phosphate buffer pH 7.5 (buffer stage)
Sampling Times: 30, 60 and 120 minutes (acid stage)
15, 30, 45 and 60 minutes (buffer stage)

Sincerely yours,

/S/

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

CC: ANDA #75-339
ANDA DUPLICATE
DIVISION FILE
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DRUG FILE

Endorsements: (Draft and Final with [illegible]s)
HFD-658 /Reviewer M. Makary /S/
HFD-658 /Bio Team Leader B. Davit /S/
HFD-617/Project Manager
HFD-650/Dale Conner /S/

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BIOEQUIVALENCY - DEFICIENCIES Submission Date: February 3, 1999

OK BMD 1. **FASTING STUDY** (STF) Strengths: 500 mg
Clinical: ~~~~ **Outcome: IC**
Analytical: ~~~~~~~~~~~~~~~~~~~~

Outcome Decisions:
IC - Incomplete

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-339

ADMINISTRATIVE DOCUMENTS

DIVISION REVIEW SUMMARY

ANDA: 75-339

DRUG PRODUCT: Sulfasalazine Delayed Release Tablets, USP

FIRM: Vintage Pharmaceutical Co.

DOSAGE FORM: Tablets

STRENGTH: 500 mg

CGMP STATEMENT/EIR UPDATE STATUS:
EER Acceptable on 10/19/99

BIO INFORMATION: Acceptable on 5/31/00.

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

The drug substance testing is 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 [redacted] method. The [redacted] method developed is stability indicating, uses a [redacted] system including an [redacted] set at [redacted] column. The mobile phase is made up of [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

Disintegration min.	No cracking in gastric fluid, NMT
Assay USP	
Dissolution USP	NLT — (Q) in 60 min.
	NMT
Impurity Limit Tests	
Impurity X	NMT
Impurity Y	NMT
	NMT
Related Substances	
Other Impurities	NMT
Total Impurities	NMT

The firm included 3 months of accelerated data at 40°C/75% RH for lot #04116. Data for both container configurations 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 a 24 month expiration dating period.

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

/S/

LABELING
The labeling review is acceptable on 4/4/~~00~~ 01.

STERILIZATION VALIDATION
NA

SIZE OF DEMONSTRATION BATCH

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

See above.

RECOMMENDATION: Approve

SIGNATURE: [illegible] 4/23/01 DATE: 11/7/00

F/T by pah/4/19/01
V:\firmsnz\vintage\ltrs&rev\75339dsf

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-339

CORRESPONDENCE

Vintage
Pharmaceuticals, Inc.

3241 Woodpark Boulevard
Charlotte, NC 28206

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

Re: ANDA# 75-339
Sulfasalazine Delayed Release 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 June 8, 2001. 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 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.

CENTER FOR DRUG EVALUATION AND RESEARCH
DEC 14 2001
OGD

Christopher J. Nascone
Regulatory Affairs

ANDA 75-339

JUN -8 2001

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 February 20, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Sulfasalazine Delayed-release Tablets USP, 500 mg.

Reference is also made to your amendments dated February 19, March 27, and May 10, 2001.

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). This is 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,

/S/ 6/8/01

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

APPEARS THIS WAY
ON ORIGINAL

noted
/ps 5/17/01

3241 Woodpark Blvd.
Charlotte, NC 28206

Vintage
Pharmaceuticals, Inc.

(704) 596-0516

May 10, 2001

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

V/AM

ORIG AMENDMENT

Re: ANDA #75-339
Sulfasalazine Delayed Release Tablets, USP
500 mg
Fax 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 May 3, 2001 from Dr. Karen Bernard of FDA and consists of revised stability protocols, laboratory test procedures, and specification pages (the impurities limits have 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.

(256) 859-2222
Huntsville, Alabama

CENTER FOR DRUG
RECD
MAY 11 2001
OGD
EVALUATION AND RESEARCH

Sincerely,
VINTAGE PHARMACEUTICALS, INC.

CJ Nascone

Christopher J. Nascone
Regulatory Affairs

5/11/01

3241 Woodpark Blvd.
Charlotte, NC 28206

Vintage Pharmaceuticals, Inc.

(704) 596-0516

March 27, 2001

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

CMC AMENDMENT
AF

Re: ANDA# 75-339
Sulfasalazine Delayed Release 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 labeling deficiency letter dated March 13, 2001.

The archival copy of the amendment consists of one volume. The review copy consists of one red-jacketed 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
DFRIP
MAR 28 2001
OGD

3241 Woodpark Blvd.
Charlotte, NC 28206

Vintage
Pharmaceuticals, Inc.

(704) 596-0516

February 19, 2001

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

[illegible] DRUG AMENDMENT

Re: ANDA# 75-339
Sulfasalazine Delayed Release 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 February 2, 2001 from Ms. Kassandra Sherrod.

The archival copy of the amendment consists of one volume. The review copy consists of one red-jacketed 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
RECD
FEB 2 0 2001
OGD
EVALUATION AND RESEARCH

3241 Woodpark Blvd.
Charlotte, NC 28206

Vintage
Pharmaceuticals, Inc.

(704) 596-0516

October 11, 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# 75-339
Sulfasalazine Delayed Release 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 volume and one separately bound, orange-jacketed bioequivalence volume. The following items are included immediately following the NDA Form 356h:

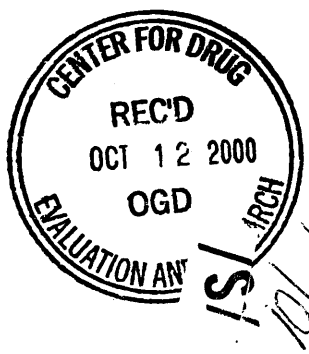
-Field Copy Certification

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



noted 8/31/00 CJ

3241 Woodpark Blvd.
Charlotte, NC 28206

Vintage Pharmaceuticals, Inc.

(704) 596-0516

August 25, 2000

NDA ORIG AMENDMENT
N/Ans

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

Re: ANDA# 75-339
Sulfasalazine Delayed Release 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 the minor deficiency letter dated August 25, 2000.

The archival copy of the amendment consists of one volume. The review copy consists of one red-jacketed 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

CJ

3241 Woodpark Blvd.
Charlotte, NC 28206

Vintage Pharmaceuticals, Inc.

(704) 596-0516

NDA ORIG AMENDMENT
N/Am

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# 75-339
Sulfasalazine Delayed Release 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 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
OCT 12 2000
OGD

/S/

3241 Woodpark Blvd.
Charlotte, NC 28206

Vintage
Pharmaceuticals, Inc.

(704) 596-0516

ORIG AMENDMENT
N/AB

March 30, 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# 75-339
Sulfasalazine Delayed Release Tablets, USP
500 mg
Bioequivalence 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 the bioequivalence deficiency letter dated September 3, 1999. We have enclosed a copy of the completed post-prandial bioequivalence study. This study was previously submitted to FDA as part of Vintage's response on February 9, 1999 to FDA's refuse to file letter dated April 1, 1998.

The archival copy of the amendment consists of two volumes. The review copy consists of two separately bound, orange-jacketed bioequivalence volumes. 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

3241 Woodpark Blvd.
Charlotte, NC 28206

Vintage
Pharmaceuticals, Inc.

(704) 596-0516

March 29, 2000

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

NDA ORIG AMENDMENT
AC

Re: ANDA# 75-339
Sulfasalazine Delayed Release 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 Delayed Release Tablets, USP
500 mg

This amendment is in response to a major deficiency letter dated March 28, 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

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
MAR 31 2000
OGD

3241 Woodpark Blvd.
Charlotte, NC 28206

Vintage
Pharmaceuticals, Inc.

(704) 596-0516

March 10, 2000

FA
TPL

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

Re: ANDA# 75-339
Sulfasalazine Delayed-Release Tablets, USP
500 mg
Fax 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 Delayed-Release Tablets, USP
500 mg

This amendment is in response to a fax request dated March 7,2000.

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:

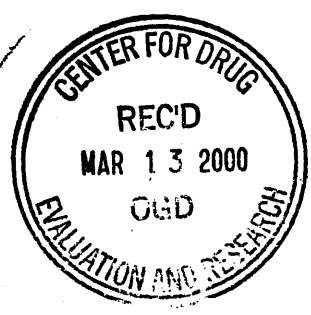
-Field Copy Certification

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



1236 Jordan Road
Huntsville, AL 35811

Vintage
Pharmaceuticals, Inc.

Phone (256) 859-2515
Fax (256) 859-2903

June 4, 1999

ORIG 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 Delayed – release 500mg Tablets
ANDA 75-339
Bioequivalence Deficiency

In response to your April 19, 1999 bioequivalency deficiency letter, Vintage offers the following responses:

OBSERVATION #1 **Please submit data to support the long-term stability of sulfapyridine in frozen study samples for the period equal to the time from the first sample collection to the day the last sample was analyzed (40 days).**

RESPONSE #1 Long term stability data for sulfapyridine in plasma covering a period of approximately 3.5 months shows excellent stability. Data submitted as Attachment 1.

OBSERVATION #2 **Please submit a post-prandial bioequivalence study on your Sulfasalazine Delayed – release Tablets, 500mg. Concentrations of Sulfasalazine sand sulfapyridine should be determined for the plasma samples collected following administration of the drug. The Division of Bioequivalence has recently changed the criteria by which bioequivalence of Sulfasalazine drug products are established. Both parent and metabolite should pass point estimate criteria for bioequivalence in a post – prandial bioequivalence study.**

RESPONSE #2 The Sulfasalazine bioequivalence study was performed over 12 months ago. The requirement for the parent and metabolite was not published or in effect at this time. When Vintage was informed, April 1, 1998 that a food study was required, there was no notice or indication of a requirement for the analysis of both metabolites. There is very little

APPEARS THIS WAY
ON ORIGINAL

sulfasalazine absorbed and the activity is minimal if any compared to the metabolite, sulfapyridine. Because this most recent change in requirements was made effective more than one year after Vintage successfully completed the bioequivalence study according to the then approved guideline, Vintage respectfully requests a waiver of the requirement to analyze both analytes.

OBSERVATION #3 **You conducted the dissolution testing using phosphate buffer pH 7.5 (buffer stage) with no prior testing in acid media (acid stage) as recommended by USP for Delayed – release (Enteric – coated) products. You are advised to submit comparative dissolution testing on your Sulfasalazine Delayed – release Tablets, 500mg using the following method:**

Apparatus: **USP XXIII 1(basket) 100 rpm**
900 ml of 0.1N HCL at 37 C for 2 hours (acid stage)
900 ml of phosphate buffer pH 7.5 (buffer stage)

Sampling **Times: 30, 60 and 120 minutes (acid stage)**
15, 30, 45 and 60 minutes (buffer stage)

RESPONSE #3 Please find enclosed as Attachment II the comparative dissolution data obtained in compliance with the USP recommendation.

Sincerely,

Becky Childers

NDA ORIG AMENDMENT
AB

3241 Woodpark Blvd.
Charlotte, NC 28206

Vintage
Pharmaceuticals, Inc.

(704) 596-0516

March 25, 1999

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

BIOEQUIVALENCE DISKETTE

Dear Sir:

As per our phone conversation of March 24, 1999, please find enclosed the bioequivalence data diskette for the fast study for the Abbreviated New Drug Application for:

Sulfasalazine Delayed Release 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.

RClda

Rebecca Childers
Manager, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

RECEIVED
MAR 29 [illegible]
GENERIC DRUGS

3241 Woodpark Blvd.
Charlotte, NC 28206

Vintage Pharmaceuticals, Inc.

(704) 596-0516

505(j)(2)(A) OK
/S/ 3/5/99 /S/

NDA ORIG AMENDMENT
N/AC

February 3, 1999

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 response to your "refusal to file" letter dated April 1, 1998, Vintage has the following comments:

Observation: The concentration of the _____ in your _____ previously approved by the Agency in an oral drug product. Therefore, the proposed drug product cannot be accepted for filing as an ANDA. Please provide examples of approved drug prodcuts administered by the same route of administration which contain this inactive ingredient in the same concentrtion range or provide information demonstrating that this inactive ingredient does not affect the safety of the proposed drug product.

Response: According to the Handbook of Pharmaceutical Excipients there are no safety issues concerning _____ is regarded as a nontosic and nonirritant material. Per the handbook the establishment of an acceptable daily intake for _____ has been thought to be unnecessary.

See Attachment I

Observation : You have failed to address the I-165 exclusivity expiring October 17, 1999

Response: See Attachment II

Observation: Please revise your Basis for ANDA submission page to reflect the correct strength of your proposed drug product and the existing exclusivity.

Respone: See Attachment III

Observation: You have failed to provide a cGLP statement for your contract test facility,

Response: See Attachment IV

Observation: In addition, the bioequivalence study submitted to support the approval of your application has been determined to be incomplete. You have failed to provide an in vivo

RECEIVED
FEB 12 1999
GENERIC DRUGS

APPEARS THIS WAY
ON ORIGINAL

bioequivalence study under fed conditons for your proposed drug product.

Response: See Attachment V

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

APPEARS THIS WAY
ON ORIGINAL

ANDA 75-339

APPEARS THIS WAY ON ORIGINAL

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

MAR 10 1999

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 our "Refuse to File" letter dated April 1, 1998 and your amendment dated February 3, 1999.

NAME OF DRUG: Sulfasalazine Delayed-release Tablets USP, 500 mg

DATE OF APPLICATION: February 20, 1998

DATE (RECEIVED) ACCEPTABLE FOR FILING: February 12, 1999

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,

/S/

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

ANDA 75-339

APPEARS THIS WAY
ON ORIGINAL

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

APR 1 1998

Dear Madam:

Please refer to your abbreviated new drug application (ANDA) dated February 20, 1998, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Sulfasalazine Delayed-release Tablets USP, 500 mg.

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to file this ANDA under 21 CFR 314.101(d)(2) for the following reasons:

The [redacted] in your proposed drug product exceeds the maximum [redacted] previously approved by the Agency in an oral drug product. Therefore, the proposed drug product cannot be accepted for filing as an ANDA. Please provide examples of approved drug products administered by the same route of administration which contain this inactive ingredient in the same concentration range or provide information demonstrating that this inactive ingredient does not affect the safety of the proposed drug product.

You have failed to address the I-165 exclusivity expiring October 17, 1999.

Please revise your Basis for ANDA Submission page to reflect the correct strength of your proposed drug product and the existing exclusivity.

You have failed to provide a cGLP statement for your

Thus, it will not be filed as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

In addition, the bioequivalence study submitted to support the approval of your application has been determined to be incomplete. You have failed to provide an *in vivo* bioequivalence study under fed conditions for your proposed drug product. If you have questions regarding your bioequivalence study, or bioequivalence requirements for this product, please contact Lizzie Sanchez, Pharm.D., Project Manager, Division of Bioequivalence, at (301) 827-5847 for further guidance.

Within 30 days of the date of this letter you may amend your application to include the above information or request in writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If after the informal conference, you still do not agree with our conclusion, you may make a written request to file the application over protest, as authorized by 21 CFR 314.101(a)(3). If you do so, the application shall be filed over protest under 21 CFR 314.101(a)(2). The filing date will be 60 days after the date you requested the informal conference. If you have any questions please call:

Gregory S. Davis
Project Manager
(301) 827-5862

Sincerely yours,

/s/ 11

Jerry Phillips
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

February 20, 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 Delayed Release, Enteric Coated Tablets, USP
500mg

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

The archival copy of the ANDA consists of four volumes. The review copy consists of two red-jacketed chemistry & manufacturing volumes and three 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. Jim Spencer, General Manager, at Tel. (704) 596-0516.

Sincerely,
VINTAGE PHARMACEUTICALS, INC.

Rebecca A. Thurman
Manager, Regulatory Affairs