CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75305

APPROVAL LETTER

ANDA 75-305

SEP 28 [illegible]

Bedford Laboratories
Attention: Shahid Ahmed
270 Northfield Road
Bedford, Ohio 44146

Dear Sir:

This is in reference to your abbreviated new drug application dated December 30, 1997, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Haloperidol Decanoate Injection, 100 mg (base)/mL.

Reference is also made to your amendments dated June 12 and August 12, 1998.

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 Haloperidol Decanoate Injection, 100 mg (base)/mL to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Haldol Decanoate - 100 Injection, 100 mg (base)/mL, of RW Johnson Pharmaceutical Research Institute).

Under 21 CFR 314.70, 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/

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

9-28-98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75305

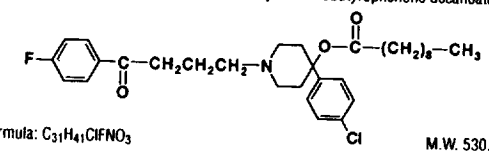
DRAFT FINAL PRINTED LABELING

HALOPERIDOL DECANOATE INJECTION

For IM Injection Only

DESCRIPTION

Haloperidol decanoate is the decanoate ester of the butyrophenone, haloperidol. It has a markedly extended duration of effect. It is available in sesame oil in sterile form for intramuscular (IM) injection. The structural formula of haloperidol decanoate, 4-[4-(*p*-chlorophenyl)-4-hydroxypiperidino]-4'-fluorobutyrophenone decanoate, is:



Molecular Formula: $C_{31}H_{41}ClFNO_3$ M.W. 530.13

Haloperidol decanoate is almost insoluble in water (0.01 mg/mL), but is soluble in most organic solvents.

Each mL of Haloperidol Decanoate Injection, 100 mg/mL, contains 141.04 mg haloperidol decanoate, equivalent to 100 mg haloperidol, in a sesame oil vehicle, with 1.2% (w/v) benzyl alcohol as a preservative.

CLINICAL PHARMACOLOGY

Haloperidol decanoate is the long-acting form of haloperidol. The basic effects of haloperidol decanoate are no different from those of haloperidol with the exception of duration of action. Haloperidol blocks the effects of dopamine and increases its turnover rate; however, the precise mechanism of action is unknown.

Administration of haloperidol decanoate in sesame oil results in slow and sustained release of haloperidol. The plasma concentrations of haloperidol gradually rise, reaching a peak at about 6 days after the injection, and falling thereafter, with an apparent half-life of about three weeks. Steady state plasma concentrations are achieved after the third or fourth dose. The relationship between dose of haloperidol decanoate and plasma haloperidol concentration is roughly linear for doses below 450 mg. It should be noted, however, that the pharmacokinetics of haloperidol decanoate following intramuscular injections can be quite variable between subjects.

INDICATIONS AND USAGE

Haloperidol Decanaote Injection, is a long-acting parenteral antipsychotic drug intended for use in the management of patients requiring prolonged parenteral antipsychotic therapy (e.g., patients with chronic schizophrenia).

CONTRAINDICATIONS

Since the pharmacologic and clinical actions of Haloperidol Decanoate Injection, are attributed to haloperidol as the active medication, **CONTRAINDICATIONS**, **WARNINGS**, and additional information are those of haloperidol, modified only to reflect the prolonged action.

Haloperidol is contraindicated in severe toxic central nervous system depression or comatose states from any cause and in individuals who are hypersensitive to this drug or have Parkinson's disease.

WARNINGS

Tardive Dyskinesia - A syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, antipsychotic drugs should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that 1) is known to respond to antipsychotic drugs, and 2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on antipsychotics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome. (For further information about the description of tardive dyskinesia and its clinical detection, please refer to **ADVERSE REACTIONS**.)

Neuroleptic Malignant Syndrome (NMS) - A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs) and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Hyperpyrexia and heat stroke, not associated with the above symptom complex, have also been reported with haloperidol.

General - A number of cases of bronchopneumonia, some fatal, have followed the use of antipsychotic drugs, including haloperidol. It has been postulated that lethargy and decreased sensation of thirst due to central inhibition may lead to dehydration, hemoconcentration and reduced pulmonary ventilation. Therefore, if the above signs and symptoms appear, especially in the elderly, the physician should institute remedial therapy promptly.

Although not reported with haloperidol, decreased serum cholesterol and/or cutaneous and ocular changes have been reported in patients receiving chemically-related drugs.

PRECAUTIONS

Haloperidol decanoate should be administered cautiously to patients:

- with severe cardiovascular disorders, because of the possibility of transient hypotension and/or precipitation of anginal pain. Should hypotension occur and a vasopressor be required, epinephrine should not be used since haloperidol may block its vasopressor activity, and paradoxical further lowering of the blood pressure may occur. Instead, metaraminol, phenylephrine or norepinephrine should be used.
- receiving anticonvulsant medications, with a history of seizures, or with EEG abnormalities, because haloperidol may lower the convulsive threshold. If indicated, adequate anticonvulsant therapy should be concomitantly maintained.
- with known allergies, or with a history of allergic reactions to drugs.
- receiving anticoagulants, since an isolated instance of interference occurred with the effects of one anticoagulant (phenindione).

If concomitant antiparkinson medication is required, it may have to be continued after haloperidol decanoate is discontinued because of the prolonged action of haloperidol decanoate. If both drugs are discontinued simultaneously, extrapyramidal symptoms may occur. The physician should keep in mind the possible increase in intraocular pressure when anticholinergic drugs, including antiparkinson agents, are administered concomitantly with haloperidol decanoate.

In patients with thyrotoxicosis who are also receiving antipsychotic medication, including haloperidol decanoate, severe neurotoxicity (rigidity, inability to walk or talk) may occur.

When haloperidol is used to control mania in bipolar disorders, there may be a rapid mood swing to depression.

Information for Patients

Haloperidol decanoate may impair the mental and/or physical abilities required for the performance of hazardous tasks such as operating machinery or driving a motor vehicle. The ambulatory patient should be warned accordingly.

The use of alcohol with this drug should be avoided due to possible additive effects and hypotension.

Drug Interactions

An encephalopathic syndrome (characterized by weakness, lethargy, fever, tremulousness and confusion, extrapyramidal symptoms, leukocytosis, elevated serum enzymes, BUN, and FBS) followed by irreversible brain damage has occurred in a few patients treated with lithium plus haloperidol. A causal relationship between these events and the concomitant administration of lithium and haloperidol has not been established; however, patients receiving such combined therapy should be monitored closely for early evidence of neurological toxicity and treatment discontinued promptly if such signs appear.

As with other antipsychotic agents, it should be noted that haloperidol may be capable of potentiating CNS depressants such as anesthetics, opiates, and alcohol.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No mutagenic potential of haloperidol decanoate was found in the Ames Salmonella microsomal activation assay. Negative or inconsistent positive findings have been obtained in *in vitro* and *in vivo* studies of effects of short-acting haloperidol on chromosome structure and number. The available cytogenic evidence is considered too inconsistent to be conclusive at this time.

Carcinogenicity studies using oral haloperidol were conducted in Wistar rats (dosed at up to 5 mg/kg daily for 24 months) and in Albino Swiss mice (dosed at up to 5 mg/kg daily for 18 months). In the rat study survival was less than optimal in all dose groups, reducing the number of rats at risk for developing tumors. However, although a relatively greater number of rats survived to the end of the study in high dose male and female groups, these animals did not have a greater incidence of tumors than control animals. Therefore, although not optimal, this study does suggest the absence of a haloperidol related increase in the incidence of neoplasia in rats at doses up to 20 times the usual daily human dose for chronic or resistant patients.

In female mice at 5 and 20 times the highest initial daily dose for chronic or resistant patients, there was a statistically significant increase in mammary gland neoplasia and total tumor incidence; at 20 times the same daily dose there was a statistically significant increase in pituitary gland neoplasia. In male mice, no statistically significant differences in incidences of total tumors or specific tumor types were noted.

Antipsychotic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients.

An increase in mammary neoplasms has been found in rodents after chronic administration of antipsychotic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Pregnancy: Teratogenic Effects: Pregnancy Category C.

Rodents given up to 3 times the usual maximum human dose of haloperidol decanoate showed an increase in incidence of resorption, fetal mortality, and pup mortality. No fetal abnormalities were observed.

Cleft palate has been observed in mice given oral haloperidol at 15 times the usual maximum human dose. Cleft palate in mice appears to be a non-specific response to stress or nutritional imbalance as well as to a variety of drugs, and there is no evidence to relate this phenomenon to predictable human risk for most of these agents.

There are no adequate and well-controlled studies in pregnant women. There are reports, however, of cases of limb malformations observed following maternal use of haloperidol along with other drugs which have suspected teratogenic potential during the first trimester of pregnancy. Causal relationships were not established with these cases. Since such experience does not exclude the possi-

bility of fetal damage due to haloperidol, haloperidol decanoate should be used during pregnancy or in women likely to become pregnant only if the benefit clearly justifies a potential risk to the fetus.

Nursing Mothers

Since haloperidol is excreted in human breast milk, infants should not be nursed during drug treatment with haloperidol decanoate.

Pediatric Use

Safety and effectiveness of haloperidol decanoate in children have not been established.

ADVERSE REACTIONS

Adverse reactions following the administration of Haloperidol Decanoate Injection, 50 mg/mL are those of haloperidol. Since vast experience has accumulated with haloperidol, the adverse reactions are reported for that compound as well as for haloperidol decanoate. As with all injectable medications, local tissue reactions have been reported with haloperidol decanoate.

CNS Effects:

Extrapyramidal Symptoms (EPS) - EPS during the administration of haloperidol have been reported frequently, often during the first few days of treatment. EPS can be categorized generally as Parkinson-like symptoms, akathisia, or dystonia (including opisthotonos and oculogyric crisis). While all can occur at relatively low doses, they occur more frequently and with greater severity at higher doses. The symptoms may be controlled with dose reductions or administration of antiparkinson drugs such as benztropine mesylate USP or trihexyphenidyl hydrochloride USP. It should be noted that persistent EPS have been reported; the drug may have to be discontinued in such cases.

Withdrawal Emergent Neurological Signs - Generally, patients receiving short term therapy experience no problems with abrupt discontinuation of antipsychotic drugs. However, some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal. In certain of these cases the dyskinetic movements are indistinguishable from the syndrome described below under "Tardive Dyskinesia" except for duration. Although the long acting properties of haloperidol decanoate provide gradual withdrawal, it is not known whether gradual withdrawal of antipsychotic drugs will reduce the rate of occurrence of withdrawal emergent neurological signs.

Tardive Dyskinesia - As with all antipsychotic agents haloperidol has been associated with persistent dyskinesias. Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The risk appears to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patients appear irreversible. The syndrome is characterized by rhythmical involuntary movements of tongue, face, mouth, or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities and the trunk.

There is no known effective treatment for tardive dyskinesia; antiparkinson agents usually do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear. Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, this syndrome may be masked.

It has been reported that fine vermicular movement of the tongue may be an early sign of tardive dyskinesia and if the medication is stopped at that time the full syndrome may not develop.

Tardive Dystonia - Tardive dystonia, not associated with the above syndrome, has also been reported. Tardive dystonia is characterized by delayed onset of choreic or dystonic movements, is often persistent, and has the potential of becoming irreversible.

Other CNS Effects - Insomnia, restlessness, anxiety, euphoria, agitation, drowsiness, depression, lethargy, headache, confusion, vertigo, grand mal seizures, exacerbation of psychotic symptoms including hallucinations, and catatonic-like behavioral states which may be responsive to drug withdrawal and/or treatment with anticholinergic drugs.

Body as a Whole: Neuroleptic malignant syndrome (NMS), hyperpyrexia and heat stroke have been reported with haloperidol. (See **WARNINGS** for further information concerning NMS.)

Cardiovascular Effects: Tachycardia, hypotension, hypertension and ECG changes including prolongation of Q-T interval and ECG pattern changes compatible with the polymorphous configuration of torsades de pointes.

Hematologic Effects: Reports have appeared citing the occurrence of mild and usually transient leukopenia and leukocytosis, minimal decreases in red blood cell counts, anemia, or a tendency toward lymphomonocytosis. Agranulocytosis has rarely been reported to have occurred with the use of haloperidol, and then only in association with other medication.

Liver Effects: Impaired liver function and/or jaundice have been reported.

Dermatologic Reactions: Maculopapular and acneiform skin reactions and isolated cases of photosensitivity and loss of hair.

Endocrine Disorders: Lactation, breast engorgement, mastalgia, menstrual irregularities, gynecomastia, impotence, increased libido, hyperglycemia, hypoglycemia and hyponatremia.

Gastrointestinal Effects: Anorexia, constipation, diarrhea, hypersalivation, dyspepsia, nausea and vomiting.

Autonomic Reactions: Dry mouth, blurred vision, urinary retention, diaphoresis and priapism.

Respiratory Effects: Laryngospasm, bronchospasm and increased depth of respiration.

Special Senses: Cataracts, retinopathy and visual disturbances.

Other: Cases of sudden and unexpected death have been reported in association with the administration of haloperidol. The nature of the evidence makes it impossible to determine definitively what role, in any, haloperidol played in the outcome of the reported cases. The possibility that haloperidol caused death cannot, of course, be excluded, but it is to be kept in mind that sudden and unexpected death may occur in psychotic patients when they go untreated or when they are treated with other antipsychotic drugs.

Postmarketing Events: Hyperammonemia has been reported in a 5½ year old child with citrullinemia, an inherited disorder of ammonia excretion, following treatment with haloperidol.

OVERDOSAGE

While overdosage is less likely to occur with a parenteral than with an oral medication, information pertaining to haloperidol is presented, modified only to reflect the extended duration of action of haloperidol decanoate.

Manifestations - In general, the symptoms of overdosage would be an exaggeration of known pharmacologic effects and adverse reactions, the most prominent of which would be: 1) severe extrapyramidal reactions, 2) hypotension, or 3) sedation. The patient would appear comatose with respiratory depression and hypotension which could be severe enough to produce a shock-like state. The extrapyramidal reactions would be manifested by muscular weakness or rigidity and a generalized or localized tremor, as demonstrated by the akinetic or agitans types, respectively. With accidental overdosage, hypertension rather than hypotension occurred in a two-year old child. The risk of ECG changes associated with torsades de pointes should be considered. (For further information regarding torsades de pointes, please refer to **ADVERSE REACTIONS.**)

Treatment - Since there is no specific antidote, treatment is primarily supportive. A patent airway must be established by use of an oropharyngeal airway or endotracheal tube or, in prolonged cases of coma, by tracheostomy. Respiratory depression may be counter-

acted by artificial respiration and mechanical respirators. Hypotension and circulatory collapse may be counteracted by use of intravenous fluids, plasma, or concentrated albumin, and vasopressor agents such as metaraminol, phenylephrine and norepinephrine. Epinephrine should not be used. In case of severe extrapyramidal reactions, antiparkinson medication should be administered, and should be continued for several weeks, and then withdrawn gradually as extrapyramidal symptoms may emerge.

ECG and vital signs should be monitored especially for signs of Q-T prolongation or dysrhythmias and monitoring should continue until the ECG is normal. Severe arrhythmias should be treated with appropriate anti-arrhythmic measures.

DOSAGE AND ADMINISTRATION

Haloperidol Decanoate Injection, 50 mg/mL should be administered by deep intramuscular injection. A 21 gauge needle is recommended. The maximum volume per injection site should not exceed 3 mL. DO NOT ADMINISTER INTRAVENOUSLY.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Haloperidol Decanoate Injection, 50 mg/mL, is intended for use in chronic psychotic patients who require prolonged parenteral antipsychotic therapy. These patients should be previously stabilized on antipsychotic medication before considering a conversion to haloperidol decanoate. Furthermore, it is recommended that patients being considered for haloperidol decanoate therapy have been treated with, and tolerate well, short-acting haloperidol in order to reduce the possibility of an unexpected adverse sensitivity to haloperidol.

Close clinical supervision is required during the initial period of dose adjustment in order to minimize the risk of overdosage or reappearance of psychotic symptoms before the next injection. During dose adjustment or episodes of exacerbation of psychotic symptoms, haloperidol decanoate therapy can be supplemented with short-acting forms of haloperidol.

The dose of haloperidol decanoate should be expressed in terms of its haloperidol content. The starting dose of haloperidol decanoate should be based on the patient's age, clinical history, physical condition, and response to previous antipsychotic therapy. The preferred approach to determining the minimum effective dose is to begin with lower initial doses and to adjust the dose upward as needed. For patients previously maintained on low doses of antipsychotics (e.g., up to the equivalent of 10 mg/day oral haloperidol), it is recommended that the initial dose of haloperidol decanoate be 10 to 15 times the previous daily dose in oral haloperidol equivalents; limited clinical experience suggests that lower initial doses may be adequate.

Initial Therapy

Conversion from oral haloperidol to haloperidol decanoate can be achieved by using an initial dose of haloperidol decanoate that is 10 to 20 times the previous daily dose in oral haloperidol equivalents.

In patients who are elderly, debilitated, or stable on low doses of oral haloperidol (e.g., up to the equivalent of 10 mg/day oral haloperidol), a range of 10 to 15 times the previous daily dose in oral haloperidol equivalents is appropriate for initial conversion.

In patients previously maintained on higher doses of antipsychotics for whom a low dose approach risks recurrence of psychiatric decompensation and in patients whose long term use of haloperidol has resulted in a tolerance to the drug, 20 times the previous daily dose in oral haloperidol equivalents should be considered for initial conversion, with downward titration on succeeding injections.

The initial dose of haloperidol decanoate should not exceed 100 mg regardless of previous antipsychotic dose requirements. If, therefore, conversion requires more than 100 mg of haloperidol decanoate as an initial dose, that dose should be administered in two injections, i.e., a maximum of 100 mg initially followed by the balance in 3 to 7 days.

Maintenance Therapy

The maintenance dosage of haloperidol decanoate must be individualized with titration upward or downward based on therapeutic response. The usual maintenance range is 10 to 15 times the previous daily dose in oral haloperidol equivalents dependent on the clinical response of the patient.

HALOPERIDOL DECANOATE DOSING RECOMMENDATIONS

PATIENTS	MONTHLY 1ST MONTH	MAINTENANCE
Stabilized on low daily oral doses (up to 10 mg/day)	10 - 15x Daily Oral Dose	10-15x Previous Daily Oral Dose
Elderly or Debilitated		
High dose	20x Daily Oral Dose	10-15x Previous Daily Oral Dose
Risk of relapse		
Tolerant to oral haloperidol		

Close clinical supervision is required during initiation and stabilization of haloperidol decanoate therapy.

Haloperidol decanoate is usually administered monthly or every 4 weeks. However, variation in patient response may dictate a need for adjustment of the dosing interval as well as the dose (See **CLINICAL PHARMACOLOGY**).

Clinical experience with haloperidol decanoate at doses greater that 450 mg per month has been limited.

HOW SUPPLIED

Haloperidol Decanoate Injection, equivalent to 100 mg/mL haloperidol.

NDC 55390-413-01, 10 x 1 mL vials

NDC 55390-413-05, 5 mL multiple dose vials

Store at controlled room temperature 15° to 30°C (59° to 86°F). Do not refrigerate or freeze. **Protect from light.** Retain vial in carton until contents are used.

Rx ONLY.

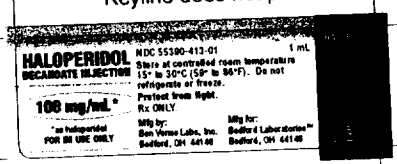
Manufactured For: Bedford Laboratories™
Bedford, Ohio 44146

Manufactured By: Ben Venue Laboratories, Inc
Bedford, Ohio 44146

June 1998

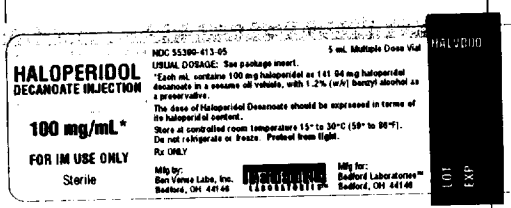
HALPA00

Keyline does not print



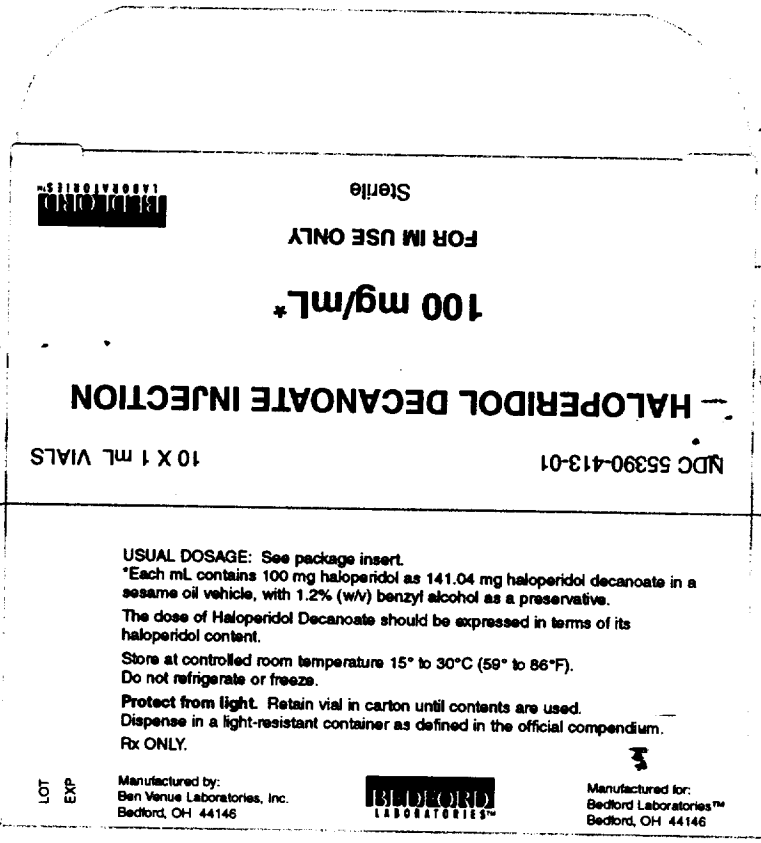
Format 66533 #117A
0.625" x 1.875"
PMS Black, PMS 283 Light Blue

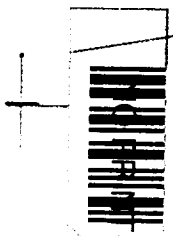
Keyline does not print



Format 66533 #118A 0.875" x 2.5"
PMS Black, PMS 283 Light Blue

1 7/8





USUAL DOSAGE: See package insert.
*Each mL contains 100 mg haloperidol as 141.04 mg haloperidol decanoate in a sesame oil vehicle, with 1.2% (w/v) benzyl alcohol as a preservative.

The dose of Haloperidol Decanoate should be expressed in terms of its haloperidol content.

Store at controlled room temperature 15° to 30°C (59° to 86°F).
Do not refrigerate or freeze.

Protect from light. Retain vial in carton until contents are used.
Dispense in a light-resistant container as defined in the official compendium.

Rx ONLY.

LOT EXP

Manufactured by:
Ben Venue Laboratories, Inc.
Bedford, OH 44146

BEDFORD LABORATORIES™

Manufactured for:
Bedford Laboratories™
Bedford, OH 44146

BEDFORD LABORATORIES™

10 X 1 mL VIALS

HALOPERIDOL
DECANOATE INJECTION

100 mg/mL*

NO PRINT

3 7/8

Format Number 66790 #041A
Black

NDC 55390-413-01

10 X 1 mL VIALS

HALOPERIDOL DECANOATE INJECTION

100 mg/mL*

FOR IM USE ONLY

Sterile

BEDFORD LABORATORIES™

HALCB00

N 3 55390-413-01 6

10 X 1 mL VIALS

HALOPERIDOL
DECANOATE INJECTION

100 mg/mL*

BEDFORD LABORATORIES™

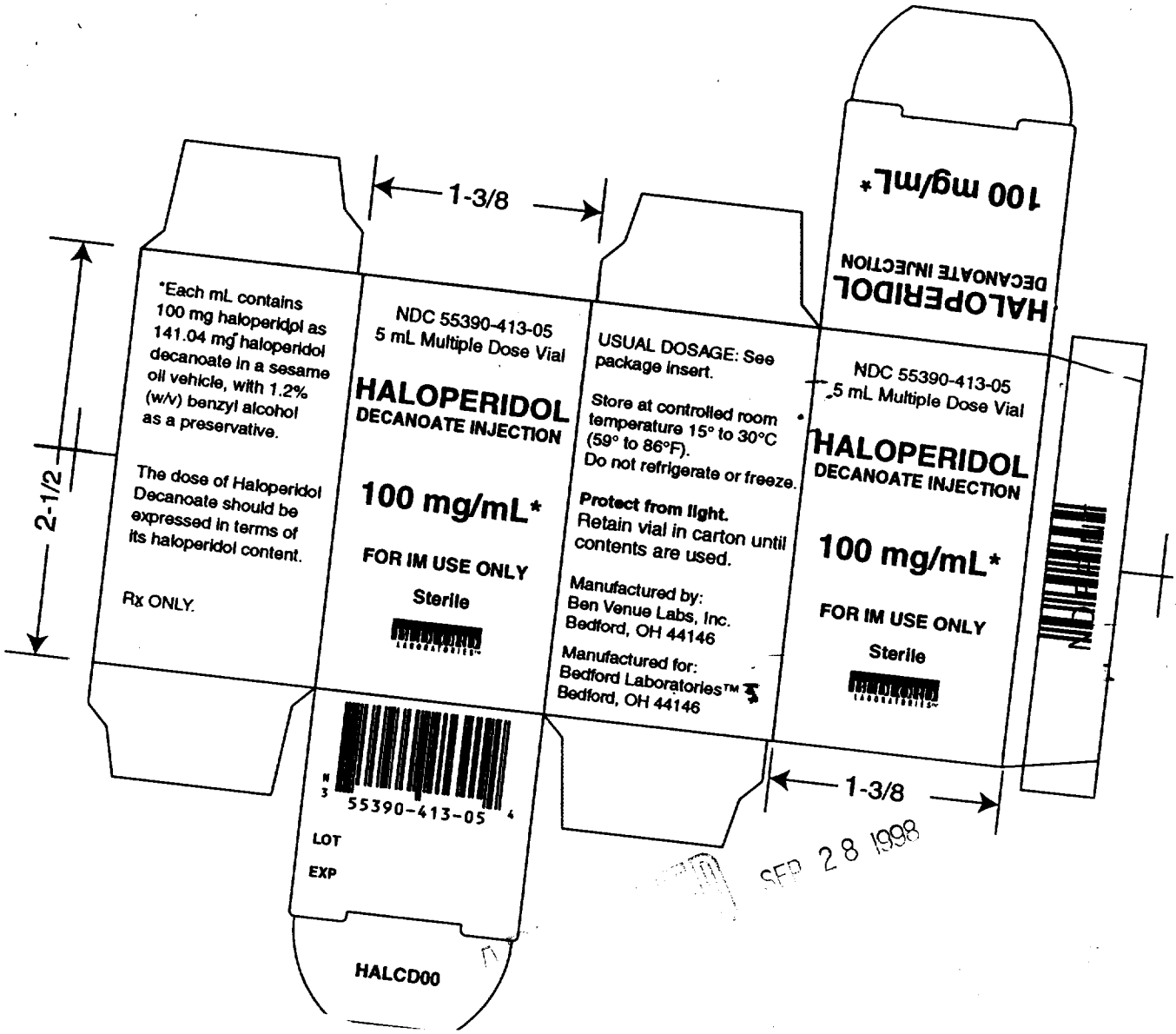
1 11/16

NO PRINT

SEP 28 1998

APPROV

BEN VENUE


1-3/8
2-1/2
*Each mL contains 100 mg haloperidol as 141.04 mg haloperidol decanoate in a sesame oil vehicle, with 1.2% (w/v) benzyl alcohol as a preservative.
The dose of Haloperidol Decanoate should be expressed in terms of its haloperidol content.
Rx ONLY.
NDC 55390-413-05
5 mL Multiple Dose Vial
HALOPERIDOL
DECANOATE INJECTION
100 mg/mL*
FOR IM USE ONLY
Sterile
55390-413-05
LOT
EXP
HALCD00
USUAL DOSAGE: See package insert.
Store at controlled room temperature 15° to 30°C (59° to 86°F).
Do not refrigerate or freeze.
Protect from light.
Retain vial in carton until contents are used.
Manufactured by:
Ben Venue Labs, Inc.
Bedford, OH 44146
Manufactured for:
Bedford Laboratories™
Bedford, OH 44146
HALOPERIDOL
DECANOATE INJECTION
100 mg/mL*
NDC 55390-413-05
5 mL Multiple Dose Vial
HALOPERIDOL
DECANOATE INJECTION
100 mg/mL*
FOR IM USE ONLY
Sterile
1-3/8
SEP 28 1998

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75305

CHEMISTRY REVIEW(S)

APPROVAL PACKAGE SUMMARY FOR 75-305

ANDA: 75-305

FIRM: Bedford Laboratories

DRUG: Haloperidol Decanoate

DOSAGE: Sterile injection

STRENGTH: 100 mg/mL; 1 mL and 5 mL vials

CGMP STATEMENT/EIR UPDATE STATUS: EER is acceptable 4/2/98

BIO STUDY/BIOEQUIVALENCE STATUS: Bio is acceptable 4/27/98

METHODS VALIDATION: The method validation for 50 mg/mL ANDA 74-811 cover the ANDA 75-305 100 mg/mL.

STABILITY: The firm has submitted satisfactory 3 months accelerated stability data at 40°C/75%RH upright and inverted and 3 months room temperature at 27.5°± 2.5°C upright and inverted for both containers.

LABELING REVIEW STATUS: Labeling satisfactory 6/23/98

STERILIZATION VALIDATION: The micro is acceptable 8/19/98

BATCH SIZES: The firm has provided the master formula and manufacturing procedure for maximum batch of . liter. Also submitted a copy of the executed batch lot #772-40-34031 of liter.
The firm will be using the same drug substance supplier and same process, and equipment.

COMMENTS: The application is approvable.

REVIEWER: Nashed E. Nashed, Ph.D. Date: 9/17/98

SUPERVISOR: Paul Schwartz, Ph.D. P.S. 9/18/98

X:\NEW\FIRMSAM\BEDFORD\LTRS&REV\75-305.SUM

1. CHEMISTRY REVIEW NO. 3

2. ANDA # 75-305

3. NAME AND ADDRESS OF APPLICANT

Bedford Laboratories
270 Northfield Rd.
Bedford, Ohio 44146

4. LEGAL BASIS FOR SUBMISSION

In the firm opinion and to the best of their knowledge, there is no patent in effect for the reference listed drug Haloperidol Decanoate. In the opinion of Bedford Laboratories, and to the best of its knowledge there is no marketing exclusivity in effect for this listed drug.

5. SUPPLEMENT(s)

Original 12/30/97

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Haloperidol Decanoate

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

Amendment 6/12/98
Amendment 8/12/98

10. PHARMACOLOGICAL CATEGORY

Antipsychotic

11. Rx or OTC

Rx

12 Related IND/NDA DMF(s)

DMF

13. DOSAGE FORM

Sterile injection

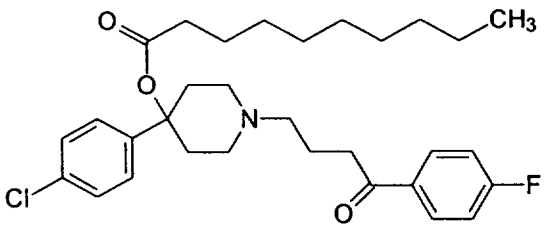
14. POTENCY

100 mg/mL; 1 mL and 5 mL vials

15. CHEMICAL NAME AND STRUCTURE

Haloperidol Decanoate. Decanoic acid, 4-(4-chlorophenyl)-1-[4-(4-fluorophenyl)-

4-oxobutyl]-4-piperidinyl ester. $C_{31}H_{41}ClFNO_3$. 530.12. 74050-97-8. Antipsychotic. USAN 1993, page 309.



16. RECORDS AND REPORTS

17. COMMENTS

Micro is satisfactory 8/19/98

18. CONCLUSIONS AND RECOMMENDATIONS

The application is approvable.

19. REVIEWER: DATE COMPLETED:

Nashed E. Nashed, Ph.D. 9/17/98

Paul Schwartz, Ph.D. 9/18/98

cc: ANDA 75-305
Division File
Field Copy

Endorsements:
HFD-627/N.Nashed, Ph.D./9-17-98 9/24/98
HFD-627/P.Schwartz, Ph.D./9-18-98 9/20/98
X:\NEW\FIRMSAM\BEDFORD\LTRS&REV\75305.3
F/T by: bc/9-23-98

Microbiology Comments to be Provided to the Applicant

ANDA: 75-305 APPLICANT: Bedford Laboratories™

DRUG PRODUCT: **Haloperidol Decanoate Injection, 100 mg/mL**

A. Microbiology Deficiencies:

1. Please provide the maximum holding time for the drug product solution.

2. Please specify the bioburden limits for the subject drug product.

3. The subject drug product is filled. You should provide the monitoring program for environment and personnel, including the alert and action limits in the application.

4. Regarding depyrogenation and sterilization:

b. Sterilization:

5. Regarding media fills, please provide a description of the media fill policy, i.e., frequency of performance, failure rate, event of failure, etc..

6. Regarding container/closure integrity-microbial ingress testing, you did not state your policy regarding leaking vials.

7. You did not provide release specifications for the subject drug product.

8. Regarding stability protocol, you should perform the antimicrobial preservative effectiveness test(APET) on the first three production lots of each dosage form.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. You may want to consider verifying the spore population and D value of the lots received from the vendor.

2. The "lots" referred to in the post approval commitment should include all sizes of the subject drug product.

Please clearly identify your amendment to this facsimile as "RESPONSE TO MICROBIOLOGY DEFICIENCIES".

Sincerely yours,

/S/

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75305

MICROBIOLOGY REVIEW

OFFICE OF GENERIC DRUGS, HFD-620
Microbiologist's Review #2
August 18, 1998

A. 1. **ANDA** 75-305

APPLICANT Bedford Laboratories™
300 Northfield Road
Bedford Ohio 44146

2. PRODUCT NAMES: **Haloperidol Decanoate Injection**

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 100 mg/mL, 1 mL in a 2 mL vial and 5 mL in 5 mL Multiple-Dose Vials, Lyophilized, Intramuscular

4. METHOD(S) OF STERILIZATION:

5. PHARMACOLOGICAL CATEGORY: Antipyschotic

B. 1. DATE OF INITIAL SUBMISSION: December 30, 1997
(Received January 2, 1998

2. DATE OF FAX AMENDMENT: August 12, 1998
Subject of this Review (Received August 13, 1998

3. RELATED DOCUMENTS: None

4. ASSIGNED FOR REVIEW: 8/17/98

C. REMARKS: The subject FAX amendment is in response to the microbiology deficiencies in the Facsimile Amendment dated August 6, 1998.

D. CONCLUSIONS: The submission is recommended for approval on the basis of sterility assurance.

/S/ 8/19/98
Andrea S. High, Ph. D.

cc: Original **ANDA**
Duplicate ANDA
Division Copy
Field Copy
Drafted by A. High, HFD 620 x:wp\microrev\75-305a
Initialed by M. Fanning, R. Patel, F. Fang, F. Holcombe, Jr.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75305

BIOEQUIVALENCY REVIEW(S)

BIOEQUIVALENCY COMMENTS

ANDA: 75-305 APPLICANT: Bedford Laboratories, Inc.

DRUG PRODUCT: Haloperidol Decanoate Injection 100 mg/mL in 1 mL and 5 mL vials.

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

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

1.1

Haloperidol Decanoate Injection
100 mg/mL, 1 mL & 5 mL Vials
ANDA #75-305
Reviewer: J. Chaney
WP# 75305w.D97

Bedford Laboratories
A Division of Ben
Venue Laboratories
Submission date:
December 30, 1997

Review of a Waiver Request for an Injectable Dosage Form

Bedford Laboratories has submitted an application for haloperidol decanoate injection 100 mg/mL and is requesting a waiver for *in-vivo* studies based on 21 CFR 320.22 (b)(1).

Haloperidol decanoate is a long-acting parenteral antipsychotic drug intended for use in the management of patients requiring prolonged parenteral antipsychotic therapy. It is supplied in two dosage strengths: 50 mg haloperidol as 70.5 mg haloperidol decanoate per mL and 100 mg haloperidol as 141.04 mg haloperidol decanoate per mL. It is administered by deep intramuscular injection. The reference listed drug is Haldol® Decanoate 100 manufactured by McNeil Pharmaceutical.

A formulation comparison is presented below:

Ingredient	**Test Bedford mg/mL**	**Reference Haldol® Decanoate 100 mg/mL**
Haloperidol Decanoate	141.04*	141.04*
Benzyl Alcohol, NF	12.0	12.0
Sesame Oil, NF	q.s.	q.s.

* equivalent to 100 mg haloperidol

Comments

1. The active ingredient, route of administration, dosage form and strength of the test drug product are the same as those of the reference listed drug.

2. All ingredients in test and reference products are qualitatively and quantitatively the same.

Recommendation

The Division of Bioequivalence agrees that the information submitted by Bedford Laboratories demonstrates that haloperidol decanoate 100 mg/mL injection falls under 21 CFR 320.22 (b)(1) of the Bioavaiiability/Bioequivalence Regulations. The waiver of an *in-vivo* bioavailability study requirement is granted. From the bioequivalence point of view the Division of Bioequivalence deems Bedford's test product bioequivalent to Haldol Decanoate 100, manufactured by McNeil Pharmaceutical.

/S/

James E. Chaney, Ph.D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHuang /S/
FT INITIALED YCHuang

Date 4/20/98

Concur: /S/

Date 4/27/98

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

JEC/041698
X:\NEW\FIRMSAM\BEDFORD\75305W.D97

cc: ANDA # 75-305 (original, duplicate), Chaney HFD-652, Drug File, Division File

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75305

CORRESPONDENCE

BEDFORD LABORATORIES™

ORIG AMENDMENT
N/FA

August 12, 1998

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

RECEIVED
AUG 13 1998
GENERIC DRUGS

RE: ANDA 75-305/Facsimile Amendment
Product: Haloperidol Decanoate Injection, 100 mg/mL

Dear Sir/Madame:

We wish to amend our unapproved Abbreviated New Drug Application, ANDA 75-305, for Haloperidol Decanoate Injection, 100mg/mL, to remove the deficiencies cited in the Facsimile Deficiency of August 6, 1998.

The number associated with the response given below corresponds to the number identifying the deficiencies listed in the communication.

A. Chemistry Deficiencies

1. The specifications for Haloperidol Decanoate Injection, 100 mg/mL, including particulate matter are presented in Attachment I.

B. Microbiology Deficiencies

1. The specifications for the maximum holding time for the drug product solution is presented in Attachment II. For liquid formulations the maximum hold time is 30 hours.

2. The bioburden alert action limits for the pre-filtered bulk formulation are as follows: Response Level 1, >10 CFU/mL and Response Level 2, >25 CFU/mL. Should any bacteria be isolated, biochemical identification testing is performed on any isolates to determine the organism's species identification. Should any fungi be isolated, a microscopic examination is performed on any mycelial for identification to Genus level as well as biochemical identification for yeasts.
Should a test result exceed Response Level 1, written notification of this event shall be distributed to appropriate parties. An investigation is initiated and should include, but

A DIVISION OF BEN VENUE LABORATORIES, INC.
300 Northfield Road • Bedford, Ohio 44146 • (440) 232-3320 • Fax (440) 232-6264

not be limited to, a review of other bioload test results, re-test of the retain sample and review of viable data associated with the Water for Injection used for the formulation of bulk solutions.
Should a test result exceed Response Level 2, in addition to the items listed above, the following activities should be performed: testing of raw materials used for the formulation of bulk solutions, review of recent raw material test results, review of sterile filtration process and a management decision as to the acceptance of the material in question.

3. The monitoring program for environment and personnel is presented on pp. 104 - 111 of the application. It summarizes the methods of testing and monitoring, Response Level 1, 2, or 3 limits, and the actions to be taken if these levels are reached. An updated revision of these pages are provided in Attachment III for your convenience.

4. Depyrogenation and Sterilization

b. Sterilization

5. The description of the media fill policy, including the frequency of performance and the actions taken due to an event of failure, is presented in Attachment VIII.

6. Container/closure integrity testing is conducted to ensure that the closure system is sufficient to prevent the microbial ingress of any bacterial organisms under "worst-case" conditions. One specification of the acceptance criteria for determining the acceptability of the closure system is that there be no detection of the test organism in the "test" vials subsequent to exposure to the microbial challenge bath. In the event that a test vial "leaks" or fails to maintain the integrity of the system an investigation is initiated in which all components of the "failed" container/closure system is closely examined. This examination is conducted to determine whether the cause of the integrity failure could be attributed to a nonconforming component (i.e. cracked or chipped vial, severed stopper, defective seal, etc). Failure of a test vial due to a nonconforming component is justification for the invalidation of that vial. In the event that the integrity failure cannot be attributed to a nonconforming component, the investigation process is continued to determine the cause of the failure and release of the container/closure system is not issued at that time.

7. The release specifications for the drug product are provided in Attachment I.

8. The revised stability protocols are presented in Attachment IX and include the antimicrobial preservative testing for the first three production lots of each dosage form.

B. Acknowledgements

1. Ben Venue Laboratories Inc. acknowledges the Agency's comments. Additionally, the Bacillus Stearothermophilus spore population obtained from the vendor is qualified according to SOP# K62.5 which is provided in Attachment X

BEDFORD LABORATORIES™

2. A corrected post approval commitment is provided in Attachment XI.

We trust this meets with your approval. If there are any questions or comments, please call the undersigned at (440)232-3320, ext. 333, or by facsimile are (440)439-6398, for any additional information.

Sincerely,
for Bedford Laboratories™

Shahid Ahmed
Director, Regulatory Affairs
Ben Venue Laboratories, Inc.

BEDFORD
LABORATORIES™

FPL

NDA ORIG AMENDMENT
N/AM

RECEIVED
JUN 15 1998
GENERIC DRUGS

June 12, 1998

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park II
7500 Standish Place, Room 150
Rockville, MD 20855

RE: ANDA 75-305/Minor Amendment
Product: Haloperidol Decanoate Injection, 100 mg/mL

Dear Sir/Madame:

We wish to amend our unapproved Abbreviated New Drug Application, ANDA 75-305, for Haloperidol Decanoate Injection, 100mg/mL, to remove the deficiencies cited in the Minor Deficiency of May 28, 1998.

The number associated with the response given below corresponds to the number identifying the deficiencies listed in the communication.

A. Chemistry Deficiencies

1. The specifications for Haloperidol Decanoate Injection, 100 mg/mL, including particulate matter and chromatogrpahic purity, are presented in Attachment I. The COA's for the exhibit lots (0772-40-34031 and 0772-44-34032) were released prior to the specifications being finalized (after review of the three month accelerated stability data). The finished product COA's have been revised as a "corrected copy" in accordance with the specifications, and are presented in Attachment I. The Pre-Approval and Post-Approval Stability Protocols have also been revised to correspond with the finished product requirements and are presented in Attachment II with the relevant stability data. Bedford Laboratories™ commits to testing all future post-approval lots in accordance with the specifications and protocols presented in Attachments I and II of this amendment

2. Notification has been received from the DMF holder that they have responded to the deficiency letter regarding DMF A copy of the letter from the DMF holder is provided in Attachment III

A DIVISION OF BEN VENUE LABORATORIES, INC.
300 Northfield Road • Bedford, Ohio 44146 • (440) 232-3320 • Fax (440) 232-6264

BEDFORD
LABORATORIES™

B. Acknowledgements

1. Bedford Laboratories™ acknowledges that the review of the microbiological section is pending.

2. Bedford Laboratories™ acknowledges that the approval of this application is dependent upon the satisfactory evaluation of cGMP compliance of all the facilities listed in the application.

C. Labeling

All deficiencies cited have been corrected. Please refer to Attachment IV for twelve copies of final printed vial labels, carton labeling, and package insert labeling (for both the 1 mL and the 5 mL vials) for review. The labels and cartons for the 5 ml vial have been included due to revisions that were made to maintain consistency with the insert and 1 mL vial. These revisions include the "Rx Only" statement and also the following statement after "Protect from light": "Retain vial in carton until contents are used". Also located in Attachment IV are annotated side-by-side comparisons of the proposed final printed labels, cartons, and insert with the last proposed labeling.

We trust this meets with your approval. If there are any questions or comments, please call the undersigned at (440)232-3320, ext. 333, or by facsimile are (440)439-6398, for any additional information.

Sincerely,
for Bedford Laboratories™

Shahid Ahmed
Director, Regulatory Affairs
Ben Venue Laboratories, Inc.