CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

20-949

Pharmacology Review(s)

Division of Pulmonary and Allergy Drug Products

Review and Evaluation of Pharmacology/ Toxicology Data

Reviewer: VE Whitehurst

HFD: HFD 570

Review Completion Date: February 22, 2001

NDA: NDA 20-949

Type of Submissions: Amendment dated October 26, 2000

Information to be conveyed to the sponsor: yes, via chemist

Sponsor: Dey Laboratories
2751 Napa Valley Corporate Drive
Napa, CA 94558

Drug: Accuneb (Albuterol sulfate inhalation solution)

Chemistry Names:
Albuterol sulfate : α1–[(tert-butylamino)methyl]-4-hydroxy-m-xylene-α, α'-diol sulfate (2:1) (salt). Molecular weight: 576.7

Relevent INDs/NDAs:
NDAs:
19-773 (Ventolin Inhalation Solution)
19-269 (Ventolin Inhalation Solution)
17-591 (Proventil Metered Aerosol)
17-853 (Proventil Tablets)
19-243 (Proventil Nebulizer Solution)

INDs:
20,926 (Ventolin)

Drug Class: Beta adrenergic agonist

Indication: [

]

Proposed Clinical Use:
Maximum daily dose for Accuneb is 5.0 mg or 0.1 mg/kg for a 50 kg person.

Route of Administration: Inhalation

Introduction and History:
This a chemistry consult from Dr. Vibhakar Shah requesting an evaluation of the proposed specification for — an impurity in the drug product, of not more than — mcg/ml. The proposed container-closure system for Accuneb is low density polyethylene (LDPE) vials overwrapped in a foil pouch. LDPE vials are fabricated from polyethylene — — which contains —

Impurity:

The sponsor is proposing a specification of — mcg/ml for — in the drug product. The maximum daily dose of 5 mg of albuterol requires 4 vials which contain 3 ml each. The maximum daily exposure to — is approximately — mcg/kg for a 50 kg person. There are no safety data for — in our database. In cases where there is no safety data, we have concluded that a daily exposure to a compound of less than — ng/kg does not require a toxicity assessment for qualification, provided the compound does not contain a structural alert for either irritancy or mutagenicity.

Recommendation:
The proposed specification for — is acceptable.

Virgil Whitehurst
Pharmacologist

CC: Division File
HFD-570/RHuff
HFD-570/VWhitehurst
HFD-570/CHKim
HFD-570/DHilfiker

/s/

Robin Huff
2/22/01 02:03:46 PM

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			REQUEST FOR CONSULTATION	
TO: *(Division/Office)* Virgil Whitehurst, Ph.D., HFD-570			FROM: Vibhakar J. Shah (HFD-820)	
DATE January 25, 2001	IND NO.	NDA NO. 20949	TYPE OF DOCUMENT Original Application	DATE OF DOCUMENT October 27, 2000
NAME OF DRUG Albuterol sulfate Inhalation Solution		PRIORITY CONSIDERATION 5	CLASSIFICATION OF DRUG S	DESIRED COMPLETION DATE February 26, 2001 Due date April 26, 2001
NAME OF FIRM Dey, L. P., 2751 Napa Valley Corporate Drive, Napa, CA 94558; Tel: (707) 224-3200, Fax: (707) 224-3235				

REASON FOR REQUEST

I. GENERAL

☐ NEW PROTOCOL	☐ PRE-NDA MEETING	☐ RESPONSE TO DEFICIENCY LETTER
☐ PROGRESS REPORT	☐ END OF PHASE II MEETING	☐ FINAL PRINTED LABELING
☐ NEW CORRESPONDENCE	☐ RESUBMISSION	☐ LABELING REVISION
☐ DRUG ADVERTISING	☐ SAFETY/EFFICACY	☐ ORIGINAL NEW CORRESPONDENCE
☐ ADVERSE REACTION REPORT	☐ PAPER NDA	☐ FORMULATIVE REVIEW
☐ MANUFACTURING CHANGE/ADDITION	☐ CONTROL SUPPLEMENT	☐ OTHER *(Specify below)*
☐ MEETING PLANNED BY		

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW	☐ CHEMISTRY
☐ END OF PHASE II MEETING	☐ PHARMACOLOGY
☐ CONTROLLED STUDIES	☐ BIOPHARMACEUTICS
☐ PROTOCOL REVIEW	☐ OTHER
☐ OTHER	

III. BIOPHARMACEUTICS

☐ DISSOLUTION	☐ DEFICIENCY LETTER RESPONSE
☐ BIOAVAILABLITY STUDIES	☐ PROTOCOL-BIOPHARMACEUTICS
☐ PHASE IV STUDIES	☐ *IN-VIVO* WAIVER REQUEST

IV. DRUG EXPERIENCE

☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL	☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES	☐ SUMMARY OF ADVERSE EXPERIENCE
☐ CASE REPORTS OF SPECIFIC REACTIONS *(List below)*	☐ POISON RISK ANALYSIS
☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP	

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS *(Attach additional sheets if necessary)*:

The proposed container-closure system (CCS) for this drug product is LDPE vials overwrapped in a foil- pouch. LDPE Vials are fabricated from polyethylene — which contains — Applicant has proposed the following limit for — in the incoming lots of — **Please evaluate the toxicity of — at the proposed specification.**

The components of the — and levels of — observed in several lots of this — are provided on the attached pages.

CC: ☒ Orig. NDA 20949	☒ HFD-570 Div. File	☒ CSO/DHilfiker	☒ Chemist/ VShah	☒ Chemistry TL/GPoochikian
SIGNATURE OF REQUESTER			METHOD OF DELIVERY *(Check one)* ☐ MAIL ☐ HAND	
SIGNATURE OF RECEIVER			SIGNATURE OF DELIVERER	

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/s/

Guiragos Poochikian
1/26/01 02:50:59 PM

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LST for RLM 5-15-00

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			REQUEST FOR CONSULTATION	
TO: *(Division/Office)* Virgil Whitehurst, Ph.D., HFD-570			FROM: Vibhakar J. Shah (HFD-820)	
DATE May 12, 2000	IND NO.	NDA NO. 20949	TYPE OF DOCUMENT Original Application	DATE OF DOCUMENT December 03, 1999
NAME OF DRUG Albuterol sulfate Inhalation Solution		PRIORITY CONSIDERATION 5	CLASSIFICATION OF DRUG S	DESIRED COMPLETION DATE May 22, 2000 (Due date June 02, 2000)
NAME OF FIRM Dey, L. P., 2751 Napa Valley Corporate Drive, Napa, CA 94558; Tel: (707) 224-3200, Fax: (707) 224-3235				

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V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS *(Attach additional sheets if necessary)*:

The proposed container-closure system (CCS) for this drug product is LDPE vials with [redacted] overwrapped in a foil pouch. **This is the first application that proposes to use paper labels directly on the LDPE vial as opposed to [redacted] the vial.** Applicant has performed extractable studies on these components by [redacted] methods. Applicant claims no significant presence of these components as leachables in the drug product. The limit of detection and limit of quantitation of the HPLC method used to analyze the samples are provided below. **Please evaluate the toxicity of these compounds at their proposed detection and quantitation levels.**

[redacted]

The components and composition of each CCS component are provided on the following pages.

CC: ☒ Orig. NDA 20949 ☒ HFD-570 Div. File ☒ CSO/DHilfiker	☒ Chemist/ VShah ☒ Chemistry TL/GPoochikian
SIGNATURE OF REQUES	METHOD OF DELIVERY *(Check one)* ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER 05/12/2000	SIGNATURE OF DELIVERER

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/s/

Virgil Whitehurst 4-19-00
Pharmacologist

CC: Division File
HFD-570/RHuff
HFD-570/VWhitehurst
HFD-570/VShah
HFD-570/DHilfiker

/s/ 4-19-00

JAN 1 1 1999

Division of Pulmonary Drug Products

Review and Evaluation of Pharmacology /Toxicology Data

Reviewer : VE Whitehurst

HFD: HFD 570

Review Completion Data : January 11, 1999

NDA: NDA 20, 949

Type of Submission : Chemistry consult dated December 15, 1998

Information to be conveyed to the sponsor: Yes

Sponsor :Dey Laboratories

Drug: Albuterol Sulfate Inhalation Solution

Druh Class: Beta adrenergic agonist

Indication: —

Route: Inhalation

Introduction and History:
Sponsor has identified these impurities in the drug substance which are above the threshold:

[ ]

The sponsor claims that these impurities have been qualified based on the results of a sub chronic toxicity study in the rat.
The sponsor did not include the data from rat sub chronic study in the submission, however, the margin of safety — was approximately — while the margin of safety for — was approximately —. In the study, the drug was given subcutaneously.

Comments:
The 30 day sub chronic study in the rat does not qualifiy these impurities because the drug was not given by inhalation and because the margins of safetywere very narrow. Additionally, the sponsor did not include any data on the genotoxic potential of these impurities.

Recommendation:
Sponsor should qualify the higher threshold for the impurities by carrying out a 90 day sub chronic toxicity study in an animal species in which albuterol is administered by inhalation. Highest dose in the study should be 10-20 times the maximum daily recommended clinical dose.

Sponsor should submit genotoxic data (point mutation, chromosomal aberration) for these impurities.

Conclusion:
The recommendations should be conveyed to the sponsor.

/S/
Virgil Whitehurst
Pharmacologist 1/11/99

CC:
Division File
HFD-570/VWhitehurst
HFD-570/Shah
HFD-570/DHilfiker

Comments:

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			REQUEST FOR CONSULTATION	
TO: *(Division/Office)* Virgil Whitehurst, Ph.D., HFD-570			FROM: Vibhakar J. Shah (HFD-820)	
DATE December 15, 1998	IND NO.	NDA NO. 20949	TYPE OF DOCUMENT Original Application	DATE OF DOCUMENT March 27, 1998
NAME OF DRUG Albuterol sulfate Inhalation Solution		PRIORITY CONSIDERATION 5	CLASSIFICATION OF DRUG S	DESIRED COMPLETION DATE

NAME OF FIRM
2751 Napa Valley Corporate Drive, Napa, CA 94558; Tel: (707) 224-3200, Fax: (707) 224-3235

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V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS *(Attach additional sheets if necessary)*:

The following mpurities in the drug substance albuterol sulfate are claimed to be qualified based on the results of 30day sub-chronic toxicity studies in the rats (Reference: NDA Vol. 1.2, p 66). Please verify applicant's qualification claim.

[redacted]

The proposed drug substance specifications and the chemical structures of these impurities are provided on the following pages.

CC: 20949 ☒ Orig. NDA ~~20949~~ ☒ HFD-570 Div. File ☒ CSO/DHilfiker	☒ Chemist/ VShah ☒ Chemistry TL/GPoochikian
SIGNATURE OF REQUEST	METHOD OF DELIVERY *(Check one)* ☐ MAIL ☒ HAND
ATURE OF RECEIVER 12.15.1998	SIGNATURE OF DELIVERER HD/C 12/16/98

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HFD 570 Division of Pulmonary Drug Products

Review of Pharmacology/Toxicology Data

Reviewer: VEWhitehurst

Review Completion Date: December 1,1998

IND/NDA: NDA 20, 949

Review Original Review- Original submission dated March 27, 1998
Supplement dated May 18, 1998
Supplement dated June 19, 1998

Information to be conveyed to the sponsor: Yes

Sponsor: Dey Laboratories
2151 Napa Valley Corporate Drive
Napa, CA 94558

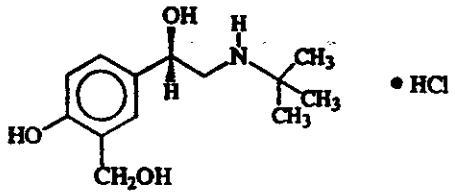
Drug: [illegible]™ (albuterol sulfate) Inhalation Solutions 0.042% and 0.021%

USAN : Albuterol sulfate

Chemical Name: 1,3 Benzenedimethanol, α^1[(1,1 dimethyethyl) amino]methyl-4-hydro, sulfate(2:1) (salt).

Cas number: 51022-70-9.

Structure:



Related INDs and DMF: IND 44,281 and DMF

Drug Class: Beta adrenergic agonist

Indication:

Clinical Formulation:

Constituents	% W/W
(0.042 %)	
Albuterol	0.42
Sodium Chloride	

Route of administration: Inhalation

Introduction and History:

The NDA was submitted under section 505 (b) of the FD&C act as (albuterol sulfate) Inhalation Solution O.0 42% and 0.21%

The NDA was submitted as a 505 (b)(2) as defined under 21 CFR 314.3 (b) which means that the sponsor can rely on preclinical data from other

marketed NDAs for albuterol. Albuterol aerosol has been approved for treatment of acute bronchospasm in patents 12 years and older since 1981 and as a dry powder since 1989. Since — is be used primarily in children, ages 6-12 years, the sponsor carried out 3 clinical trials to determine the safe and effective dose to be used in children. Albuterol has been widely used and is well established for the management of reversible obstructive airway disease in more than 30 countries.

Studies reviewed in this submission:
No preclinical studies were submitted in this NDA.

Labeling for —
The labeling for — should be amended as follows:

Clinical Pharmacology section:
Paragraph # 3 should be removed and replaced with the following:

Preclinical:
Intravenous studies in rats with albuterol sulfate have demonstrated that albuterol crosses the blood- brain barrier and reaches brain concentrations amounting to approximately 5.0% of the plasma concentrations. In structures outside the blood- brain barrier (pineal and pituitary glands), albuterol concentrations were found to be 100 times those in the whole brain.

Studies in laboratory animals (minipigs, rodents and dogs) have demonstrated the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta-agonists and methylxanthanes are administered concurrently.

Carcinogenesis, Mutagenesis and Impairment of Fertility section:
The Carcinogenesis, Mutagenesis and Impairment of fertility section should be amended as follows:
In a 2 years study in Sprague-Dawley rats, albuterol sulfate caused a significant dose-related increase in the incidence of benign leiomyomas of the mesovarium at and above dietary doses of 2.0 mg/kg [redacted] the maximum recommended daily inhalation dose for [redacted]. In another study, this effect was blocked by the coadministration of propranolol, a non-selective beta -adrenergic antagonist. In an 18-month study in CD-1 mice, albuterol sulfate showed no evidence of tumorigenicity at dietary doses up to 500 mg/kg (approximately 410 times the maximum recommended daily inhalation dose [redacted] on a mg/m^2 basis [redacted]. In a 22 month study in the Golden hamster, albuterol sulfate showed no evidence of tumorigenicity at dietary doses up to 50 mg/kg [redacted]

Albuterol sulfate was not mutagenic in the Ames test [redacted]

[redacted] Albuterol sulfate was not clastogenic in a human peripheral lymphocyte assay or in an AH_1 strain mouse micronucleus assay.

Reproduction studies in rats demonstrated no evidence of impaired fertility at oral doses of albuterol sulfate up to 50 mg/kg (approximately [redacted] times the maximum recommended daily inhalation dose on a mg/m^2 basis).

Pregnancy: Teratogenic Effects—Pregnancy Category C: The Pregnancy: Teratogenic Effects section should be revised as follows:
Albuterol sulfate has been shown to be teratogenic in mice. A study in CD-1 mice [

] cleft palate formation in 5 of 111 (4.5%) fetuses. Albuterol sulfate at a sc dose of 2.5 mg/kg (approximately 2 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis), induced cleft palate formation in

[

]

There are no adequate and well-controlled studies in pregnant women.
[

] albuterol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

During worldwide marketing experience, various congenital anomalies, including cleft palate and limb defects, have been reported in the offspring

of patients being treated with albuterol. Some of the mothers were taking multiple medications during their pregnancies. No consistent pattern of defects can be discerned, a relationship between albuterol use and congenital anomalies has not be established.

Overdosage : Paragraph 2 of the overdosage section should be revised as follows:

The oral median lethal dose of albuterol sulfate in mice is greater than 2000 mg/kg (approximately — times the maximum recommended daily inhalation dose — on a mg/m^2 basis

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The calculations for the margin of safety for [redacted] are shown below:

Drug: [redacted]

	Age	mg/dose	# daily doses	mg/day	kg	mg/kg	factor	mg/m²
Pediatric	[redacted]			5	20	0.25	25	6.25
Adult	>12	[redacted]		5	50	0.10	37	3.70

	Route	mg/kg/d	conv. factor	mg/m²	Dose Ratio Adults	Dose Ratio Children	Rounded Dose Ratio Adults	Rounded Dose Ratio Children
Carcinogenicity:								
Mouse	[redacted]		3	1500	405.405	240	410	240
Mouse	[redacted]		3	0	—	—	—	—
Rat	[redacted]		6	12	3.24324	1.92	3	2
Rat	[redacted]		6	0	—	—	—	—
Hamster	[redacted]		4	200	54.0541	32	55	30
Reproduction and Fertility:								
Rat	[redacted]		6	300	81.0811	N/A	80	N/A
Rat	[redacted]		6	0	—	N/A	—	N/A
Rat	[redacted]		6	0	—	N/A	—	N/A
Extra	[redacted]		—	—	—	N/A	—	N/A
Teratogenicity:								
Mouse	[redacted]		3	0.075	0.02027	N/A	1/49	N/A
Mouse	[redacted]		3	0.75	0.2027	N/A	1/5	N/A
Mouse	[redacted]		3	7.5	2.02703	N/A	2	N/A
Rabbit	[redacted]		12	600	162.162	N/A	160	N/A
Rat	[redacted]		6	0	—	N/A	—	N/A
Overdosage:								
Mouse	[redacted]		3	6000	1621.62	960	1600	960
Mouse	[redacted]		3	0	—	—	—	—
Rat	[redacted]		6	2700	729.73	432	730	430
Rat	[redacted]		6	12000	3243.24	1920	3200	1900
Other:	(Describe studies here)							

Rat	[redacted]	6	0	—	—	—	—
Rat		6	0	—	—	—	—
Mouse		3	0	—	—	—	—
Mouse		3	0	—	—	—	—
Extra		—	—	—	—	—	—

Conversion, Correction, and Rounding Factors:

Human Age (yr)	Weight (kg)	Factor (kg/m²)	Species	Factor (kg/m²)	Exposure greater than x-times human	Round to nearest
0	3	25	dog	20	1	1
1	10	25	guinea pig	8	10	5
2	12	25	hamster	4	100	10
4	16	25	monkey	12	1000	100
6	20	25	mouse	3	10000	1000
12	50	37	rabbit	12		
			rat	6		

Impurity Problem with —

During communication with the sponsor, the FDA suggested that Dey

Dey submitted safety data from published literature. However, these data were not adequate to support the safe use of — Dey has now decided to eliminate the overwrap — and develop a different overwrap. Dey planned to submit the new overwrap plus the stability data

to their NDA in the fall . However, as of December 1, 1998, these data have not been submitted. Yesterday, Dey reported that the stability data for their new overwrap will be submitted in February.

Recommendation:

The NDA is approvable pending satisfactory resolution of [redacted] in the overwrap. The labeling revisions for [redacted] should be conveyed to the sponsor.

/S/

Virgil Whitehurst 12-8-98
Pharmacologist

cc: Divison file
HFD-570/VWhitehurst
HFD-570/TZoetis /S/ 12/21/98
HFD-570/DO'Hearn
HFD-570/DHilfiger
HFD-570/VShah

IND 44,281 JANUARY 6,1994

ORIGINAL REVIEW

JAN 6 1994

DRUG : Albuterol Sulfate Inhalation

SPONSOR : Dey Laboratories, Inc

CATEGORY : Treatment Of Asthma in Children, 6-12 years.

DATE SUBMITTED TO FDA : December 30, 1994

DATE RECEIVED BY FDA : January 3, 1994

DATE RECEIVED BY REVIEWER : January 5, 1994

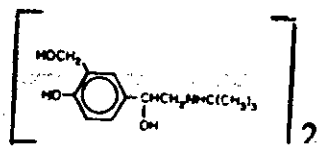
Completion Date : January 6, 1994

COMPOSITION OF ALBUTEROL SOLUTION FOR INHALATION

INGREDIENT	AMOUNT		
Albuterol Sulfate	.75 mg	1.5 mg	3.0 mg
Sodium Chloride	as required	as required	as required*
	as required	as required	as required **

*
**

CHEMICAL STRUCTURE



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RELATED NDAs : NDA — and NDA —

PROPOSED CLINICAL TRIAL

The current clinical plan includes a dose ranging study and a treatment plan. The dose ranging study will be conducted to establish the dose-response curve of albuterol sulfate as a nebulized treatment for asthma in children 6 -12 years of age. The dose -range curve will be used to estimate the lowest effective dose as well as the shape, magnitude and variability of albuterol so that an appropriate dose can be identified for use in the treatment protocol.
The treatment plan will be conducted to investigate the effects of albuterol sulfate solution for inhalation in the treatment in patients 6 through 12 years.

In the dose-ranging study, 24 male and female pediatric patients with moderately severe asthma, ages 6 to 12 years will be included in this study. In the randomized 4- way crossover design, one of four nebulizer treatment (0.75 mg. 1.5 mg, 3.0 mg single doses of albuterol sulfate or placebo) will be administered (in 3mL normal saline) at each of four sessions, separated by 3-9 days.

The daily dose of albuterol in this study will be much lower than the recommended daily dose which is 2.5 mg, four times daily or a total dose of 10 mg. The single highest dose in this study will be 3 mg. This would result in a high daily dose of 0.14 mg/kg for a 6 year old weighing approximately 20 kg and a high dose of 0.08 mg/kg for a 12 old weighing 40 kg.

PRECLINICAL STUDIES

No preclinical studies were submitted in this IND. However, albuterol sulfate has been marketed for over 12 years as a treatment for asthma in adults and children over 12 years of age. In addition, albuterol has been widely studied and used in children as young as 20 months of age in doses as high as 3 mg per hour for several hours. Alternate dose forms have been established for children under 12 years of age, (2 years and older for albuterol syrup, 4 years and older for albuterol MDI and 6 years and older for albuterol tablets). The safety profile for albuterol has been well characterized in adults and children.

CONCLUSION
Study maybe initiated.

RECOMMENDATIONS :
None at this time.

/S/

Virgil Whitehurst
pharmacologist

CC :
IND-44,281
IND-DIV FILE
HFD-MED OFF/OTULANA
HFD-CSO/156
HFD-VEW
WP/VEW

/S/ 1-6-94