CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-945

CHEMISTRY REVIEW(S)

DIVISION OF ANTIVIRAL DRUG PRODUCTS

JUN 25 1999

Review of Chemistry, Manufacturing, and Controls Section

NDA #: 20-945

CHEMISTRY REVIEW #: 2

DATE REVIEWED: 25-JUN-99

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original	21-NOV-97	24-NOV-97	26-NOV-97
Amendment	28-JAN-98	29-JAN-98	
Amendment	15-MAY-98	18-MAY-98	21-MAY-98
Amendment	20-JUL-98	21-JUL-98	31-JUL-98
Amendment	28-AUG-98	31-AUG-98	09-SEP-98
Amendment	13-OCT-98	14-AUG-98	
Amendment	11-NOV-98		
Amendment (BC)	01-MAR-99	02-MAR-99	03-MAR-99
Amendment (BC)	29-APR-99	30-APR-99	07-MAY-99
Amendment (BC)	09-JUN-99		
Amendment (BC)	10-JUN-99	10-JUN-99	21-JUN-99
Amendment (BC)	10-JUN-99	10-JUN-99	23-JUN-99
Amendment (BC)	18-JUN-99		
Amendment (BC)	23-JUN-99	28-JUN-99	
Amendment (BC)	25-JUN-99	28-JUN-99	

NAME/ADDRESS OF APPLICANT: Abbott Laboratories
D-491/AP6B-1
100 Abbott Park Road
Abbott Park, IL 60064-3500

DRUG PRODUCT NAME

Proprietary: NORVIR®

Nonproprietary: Ritonavir

Code Name/#: Abbott-84538.0, ABT-538

PHARMACOLOGICAL CATEGORY: Antiviral

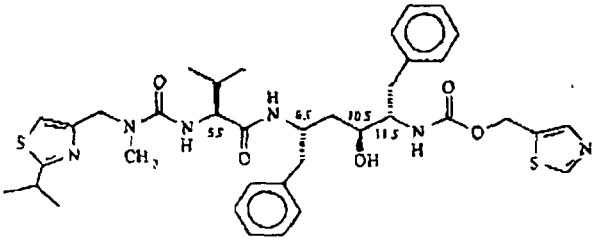
INDICATION: Treatment of HIV Infection

DOSAGE FORM/STRENGTH: Soft Gelatin Capsules, 100 mg

ROUTE OF ADMINISTRATION: PO

CHEMICAL NAME / STRUCTURAL FORMULA:

10-Hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12-tetraazatridecan-13-oic acid, 5-thiazolylmethyl ester, [5S-(5R*, 8R*, 10R*, 11R*)]-



Registry Number [155213-67-5]

$C_{37}H_{48}N_6O_5S_2$ Formula Weight: 720.95

SUPPORTING DOCUMENTS:

DMF: See table in REVIEW NOTES section.

RELATED DOCUMENTS:

NDA 20-945 (Original) Chemist review
NDA 20-659 and supplements including Supplements S014, S015 and S017
FDA Letter (NA) dated November 23, 1998 (see NDA package)
Facsimile of CMC requests of June 2, 1999 (see REVIEW NOTES, Section H.1)
Facsimile of teleconference minutes of June 16, 1999 (see NDA package)
Facsimile of teleconference minutes of June 22, 1999 ((see REVIEW NOTES, Section H.2)

CONSULT REVIEWS:

Trade name review by CDER Labeling and Nomenclature Committee
Product specific inspection of DS and DP manufacturing sites

SUMMARY OF THE APPLICATION:

Ritonavir is an inhibitor of HIV protease with activity against the human immunodeficiency virus (HIV). This drug was approved in 1996 and marketed by Abbott Laboratories as two formulations, NORVIR^R Oral Solution, 80 mg/mL and NORVIR^R Capsules, 100 mg. The capsule formulation was a semi-solid containing 100 mg ritonavir encapsulated in a hard gelatin capsule. Because ritonavir has very poor aqueous solubility, these two products were formulated with [redacted] to enhance solubility and bioavailability. Abbott subsequently developed a soft gelatin capsule for [redacted] improving room temperature stability, and reducing total daily intake of [redacted] when compared with the semi-solid capsule. The soft gelatin capsule formulation was a ritonavir solution in a [redacted] with an [redacted] filled into a soft gelatin capsule at the weight to provide for a 100 mg [redacted] label claim. The NDA for this product (20-945) was filed in November 1997.

In July 1998, Abbott notified the FDA that they had experienced manufacturing difficulties with the semi-solid capsules. During manufacturing of the product, a new polymorphic form of ritonavir (Form II) which is less soluble than the known Form I ritonavir appeared in the capsules, resulting in failure of dissolution testing. Abbott later reported that Form II also appeared in the oral solution and in the soft gelatin capsules. As a result of this problem, the semi-solid capsules were removed from the market, the shelf life and storage condition for the oral solution were changed from 24 months at 5^0 C to 6 months at 25^0 C through supplements, and the soft gelatin formulation was modified. The latter two actions were taken to ensure adequate solubility of ritonavir in these formulations. A "not approvable" action was taken on NDA 20-945 in November 1998 due to insufficient CMC data on a modified soft gelatin formulation to address the quality, stability and performance of the new product. Information required for a resubmission was recommended in the FDA letter dated November 23, 1998.

An NDA amendment was filed on March 1, 1999 for a new soft gelatin capsule, 100 mg (modified soft gelatin formulation). The CMC section of this resubmission package are summarized as follows:

A. DRUG SUBSTANCE Acceptable

CMC information for the drug substances, ritonavir, is incorporated by reference to approved NDA 20-659 for NORVIR (ritonavir oral solution), and all amendments and supplements thereto. Information on Form II has been provided through NDA 20-945 amendments and this resubmission package.

Following the discovery of ritonavir Form II, Abbott has conducted several studies to characterize the physical properties of the two polymorphic forms. Form I and II can be distinguished by [redacted] data show that Form II is more thermodynamically stable than Form I, [redacted] Polymorph screening studies conducted by an outside expert, [redacted] confirm that Form II is [redacted]. An [redacted] method was developed to screen Form II content in bulk ritonavir drug substance. At this time, the reasons for the appearance of Form II remain unknown.

Drug substance containing various percentages of Form II (from [redacted] was used in the production of a modified soft gelatin capsule formulation for primary and supportive NDA stability lots. The modified formulation was developed to [redacted]

Due to limited stability data on Form II ritonavir, FDA and Abbott have [redacted]

B. DRUG PRODUCT Acceptable

The modified soft gelatin capsule formulation was developed through minor modifications of the original soft gelatin capsule formulation without addition of any new excipients. The modifications include [redacted] addition of [redacted] to the [redacted] and a corresponding adjustment to the oleic acid amount, and [redacted] butylated hydroxytoluene (BHT) [redacted], to maintain the same total daily intake. Experiments were conducted to ensure that the modified formulation would [redacted]

NORVIR[R] soft gelatin capsules are white [redacted] capsules imprinted with corporate logo, 100 and the Abbo-Code DS. The product is available in 100 mg strength with the following inactive ingredients: Butylated hydroxytoluene, ethanol, gelatin, iron oxide, oleic acid, polyoxy35 castor oil, and titanium dioxide. Excipients and materials related to the manufacturing processes have been identified. Specifications and test methods for these inactive materials were found acceptable.

Composition for the capsule per unit and per a typical production batch of [redacted] equivalent to [redacted] capsules) was provided. Ranges (≤ ± 5%) for the excipients used were justified. Manufacturing process includes [redacted] preparation and encapsulation of the [redacted] into soft gelatin capsules. The manufacturing process and in-process controls were found acceptable. The commercial product will be manufactured at [redacted] and packaged as 120 counts/ [redacted] bottle by Abbott Laboratories at Abbott Park, North Chicago, Illinois.

[redacted] scale (commercial scale) and [redacted] scale batches of the modified formulation were manufactured at [redacted] for product registration. Executed batch records for manufacturing and for packaging were found acceptable. Certificates of Analysis (COA) for the stability batches were provided.

Stability studies were conducted on [redacted] batches and [redacted] batch of the modified capsules under the following storage conditions according to pre-approved protocols: at 5^0 C (real time), 25^0 C/60% RH (accelerated condition), [redacted]. Additional studies were conducted on [redacted] of the modified capsules manufactured with [redacted] to determine effect of [redacted] on the physical characteristics of the modified capsules. Since the production experience and the stability data for the modified capsules are limited ([redacted] for full report and [redacted] for physical stability only), long term stability data on the original soft gelatin capsules are used as supplemental information to predict the performance of the modified capsules.

Two bioavailability studies were conducted to assess the impact of [redacted] undissolved Form II ritonavir in hand-filled capsules. See biopharmaceutics review for details.

The drug product will be controlled by a set of process control limits as well as acceptance limits. Process control limits are defined as requirements that must be met during the manufacturing cycle or at product release/acceptance to assure that acceptance limits are met through the time of use or expiry period. Acceptance limits are defined as requirements that must be met at the time of product release/acceptance through the time of use or expiry period. Drug product release specifications include the following: [redacted] At this time drug product specifications were established based on the release data and stability data for the modified and the original soft gel formulation, and a comparison with the approved ritonavir products. Due to limited stability data on the modified capsules, [redacted]

An interim expiration dating period of [redacted] was granted to the modified capsules based on the existing data on the primary stability lots and supportive stability lots. FDA and Abbott have reached agreement that [redacted] in addition to the routine stability commitment to test the first 3 commercial production lots according to an accepted post approval stability protocol,

Abbott committed to [redacted] Per request, Abbott also committed to [redacted]

PHASE IV COMMITMENTS

FDA and Abbott have reached an agreement on the following Phase IV commitments:

(i) [redacted]

(ii) [redacted]

C. INVESTIGATIONAL FORMULATIONS — Described above

D. ENVIRONMENTAL ASSESSMENT — Satisfactory

A statement of Categorical Exclusion under 21 CFR 25.31(b) was amended on 9/17/97.

E. METHODS VALIDATION — Pending

F. LABELING — Acceptable

Per FDA request (7/9/98 facsimile memo), the proposed proprietary name and established name NORVIR[R] [redacted] have been revised to FDA's recommendation: NORVIR[R] (ritonavir capsules) soft gelatin. The chemistry section of the package insert was found acceptable. The draft container label was found acceptable.

G. ESTABLISHMENT INSPECTION — Acceptable

CGMP compliance status for Abbott Spa, Italy (DS manufacturer), Abbott North Chicago (DS manufacturer), [redacted], and Abbott Park (DP packager, labeler, and release tester) were found acceptable on June 19, 1998.

CONCLUSIONS/RECOMMENDATIONS:

In conclusion, this NDA is recommended for approval from the Chemistry, Manufacturing and Controls perspective.

/S/

Ko-Yu Lo, Ph.D., Review Chemist

Concurrence:
HFD-530/SMiller /S/

cc:
Orig. NDA 20-945
HFD-530/Div. File
HFD-530/KLo
HFD-530/SMiller
HFD-530/KStruble
HFD-530/SLynche
HFD-830/CChen

31 Page(s) Withheld

DIVISION OF ANTIVIRAL DRUG PRODUCTS
Review of Chemistry, Manufacturing and Controls Section

NDA #: **20-945**

CHEMISTRY REVIEW #: 1 **DATE REVIEWED:** 19-NOV-98

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
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Amendment	20-JUL-98	21-JUL-98	31-JUL-98
Amendment	28-AUG-98	31-AUG-98	09-SEP-98
Amendment	13-OCT-98	14-AUG-98	NA
Amendment	11-NOV-98		

NAME/ADDRESS OF APPLICANT: Abbott Laboratories
D-491/AP6B-1
100 Abbott Park Road
Abbott Park, IL 60064-3500

DRUG PRODUCT NAME
Proprietary: NORVIR^R
Nonproprietary: Ritonavir
Code Name/#:

PHARMACOLOGICAL CATEGORY: Antiviral

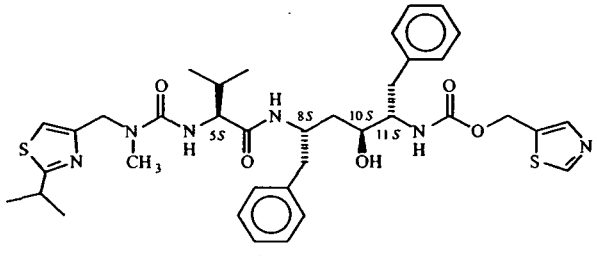
INDICATION: Treatment of HIV Infection

DOSAGE FORM/STRENGTH: Soft Gelatin Capsules, 100 mg

ROUTE OF ADMINISTRATION: PO

CHEMICAL NAME / STRUCTURAL FORMULA:

10-Hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12-tetraazatridecan-13-oic acid, 5-thiazolylmethyl ester, [5S-(5R*, 8R*, 10R*, 11R*)]-

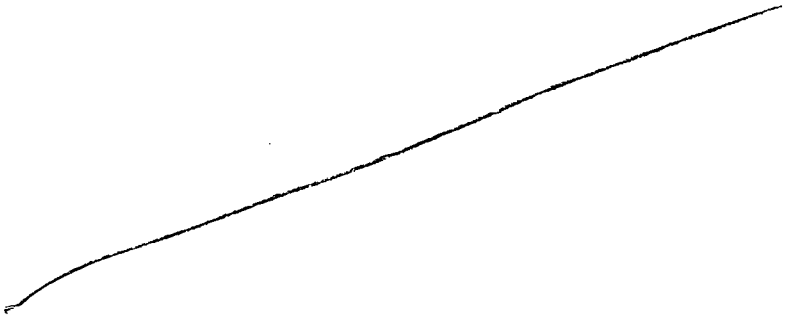


Registry Number [155213-67-5]

$C_{37}H_{48}N_6O_5S_2$ Formula Weight: 720.95

SUPPORTING DOCUMENTS:

DMF



Letters of Authorization (LOA) for cross referencing the DMFs were provided.

RELATED DOCUMENTS:

NDA 20-659 and supplements including Supplements S014, S015 and S017:
Phase I and II manufacturing process for ritonavir drug substance
Characterization of ritonavir Form II crystals
Physicochemical properties of ritonavir Form II

CONSULT REVIEWS:

Trade name review by CDER Labeling and Nomenclature Committee
Product specific inspection of DS and DP manufacturing sites

SUMMARY OF THE APPLICATION:

Ritonavir is an inhibitor of HIV protease with activity against the human immunodeficiency virus (HIV). This drug is currently marketed by Abbott Laboratories as NORVIR^R Oral Solution, 80 mg/mL, and NORVIR^R Capsules, 100 mg. The capsule formulation is a semi-solid containing 100 mg ritonavir encapsulated in a hard gelatin capsule. Because ritonavir has very poor aqueous solubility, these two products are formulated with to enhance solubility and bioavailability.

In this NDA, Abbott proposes to market a soft elastic capsule (SEC) formulation. The SEC is developed for , better room temperature stability, and reducing total daily intake of when compared with the semi-solid capsules. The SEC product is formulated as a , filled into a soft elastic gelatin capsule at the weight to provide for a 100 mg label claim. Pertinent CMC information on this product is summarized in the Comment Section following this application summary. By July 1998, review of the chemistry section was nearly completed. Outstanding issues to be discussed with Abbott include: Drug product specifications , and labeling. Due to the unexpected finding of crystal precipitation in the capsule dosage forms, an attempt to resolve these issues with Abbott was put on hold.

On July 24, 1998, Abbott met with DAVDP and indicated that they have experienced manufacturing problems with the semi-solid capsules. Samples from consecutive commercial batches manufactured in June 1998 had failed dissolution specification and crystal precipitation

was observed in these samples. The crystal precipitation is attributed to a new polymorph (Form II) of ritonavir, which is significantly less soluble than the Form I ritonavir that has been used to produce — commercial batches without failure since product launch. Abbott subsequently reported that crystal precipitation was also observed in SEC samples during validation, therefore, proposed to reformulate the original SEC. **The proposed modifications include (1) addition of — and (2) reduction of — to ensure that —** Stability study on the modified SEC and a biostudy to establish the bioequivalence between the original and modified SEC were initiated in September. In addition, the possibility of using data from simulation studies designed to address the stability of the modified SEC during manufacturing and long term storage was discussed with Abbott in a meeting on September 18, 1998.

In an amendment dated November 11, 1998 Abbott proposes a data package to support the modified SEC and a timeline for submitting these data in next two months. Following a careful review of the proposed data package, FDA viewed that the data is insufficient/inadequate to demonstrate product quality, stability and performance. Based on the following two major deficiencies, a not approvable action is recommended from a CMC standpoint:

(1) As a result of the presence of Form II ritonavir in the current manufacturing environment, CMC information on the original SEC cannot be used to justify approval of the modified SEC.

(2) The CMC data package proposed for the modified SEC does not adequately address the quality, stability and performance of the drug product.

a) — of real time stability data are insufficient to support product quality (especially freedom from crystallization) over the proposed — expiration dating period. Measurement of — beyond the — time point is especially important since — is known to be a critical factor controlling solubility.

b) Data from simulation studies designed to address the stability of the modified SEC during manufacturing and storage (i.e., — are insufficient to predict the outcome of long term storage.

Data sets required for a resubmission are as follows:

(1) A complete CMC section for the modified SEC including a minimum of — real time stability data on the registration batches at the time of resubmission, with the — stability update to be submitted during the review cycle.

(2) Final study results from Experiment 1- 6 of the October 13, 1998 submission. We would recommend a teleconference to discuss the extension of — — in Experiment 4 and 5.

Prior to this resubmission, a complete analytical package including test methods for ritonavir Form II should be amended to NDA 20-659.

COMMENTS ON THE ORIGINAL SEC:

A. DRUG SUBSTANCE Acceptable

CMC information for ritonavir drug substances is incorporated by reference to approved NDA 20-659 for NORVIR (ritonavir oral Solution), and all amendments and supplements thereto.

B. DRUG PRODUCT Acceptable pending on the establishment of drug product specifications

NORVIR[R] soft gelatin capsules are white — capsules imprinted with corporate logo, Abbo-Code — and potency. The product is available in strengths of 100 mg — ritonavir with the following inactive ingredients: Butylated hydroxytoluene (BHT), ethanol, gelatin, iron oxide, oleic acid, polyoxyl 35 castor oil, and titanium dioxide. Excipients and materials related to the manufacturing processes have been identified. Specifications and test methods for these inactive materials were found acceptable. Appropriate information has been amended to address the following excipient revisions: (i) , and (ii) change of manufacturing site for — i.e., , statement and a revised HPLC method to determine drug related impurities in SEC). Compositions for the capsules per unit and per a typical production batch of (equivalent to of the 100 mg capsules) have been provided. The manufacturing process includes — preparation and encapsulation of the — into soft elastic capsules. The manufacturing process and in-process controls (i.e., , were found acceptable. The commercial product will be manufactured at and packaged by Abbott Laboratories at their Abbott Park, Illinois facility. The 100 mg strength will be packaged as counts/bottle,

of the proposed commercial batch size) batches of have been manufactured at . Each — lots was for encapsulation into a 100 mg capsules, Batch records for manufacturing (provided in — DMF) and for packaging (provided in the NDA) were found acceptable. Certificates of Analysis (COA) for the — stability batches and the — bio batches were provided in lieu of a tabulated batch analyses. Data on the COAs were found acceptable.

Stability studies were conducted on — batches under the following conditions according to pre-approved protocols: at 5^0 C (real time), 25^0 C/60% RH (accelerated condition), — Based on the stability data for product stored at 5^0 C, an — expiration dating period was granted to drug product when stored at 5^0 C (2 –8^0 C). Based on the — 25^0 C/60%RH stability data for product stored for — at 5^0 C — , the proposed label statement of was found acceptable.

Per FDA request, revised post approval stability protocols were amended on 7/20/98 and were found acceptable.

The following two issues have not been resolved with Abbott due to the unexpected development of ritonavir Form II:

1. [redacted]

2. **Drug product specifications -- Specifications for the drug products include** [redacted]

   The limits on drug related impurities as well as the inclusion of a specification on [redacted] **have not been discussed with Abbott.**

C. INVESTIGATIONAL FORMULATIONS **Satisfactory**

D. ENVIRONMENTAL ASSESSMENT **Satisfactory**

A statement of Categorical Exclusion under 21 CFR 25.31(b) was amended on 9/17/97.

E. METHODS VALIDATION **Pending**

As a result of manufacturing site change for [redacted] the HPLC method [redacted] for determination of related substance in the SEC was found not suitable (see Abbott's memo on summary of [redacted] impurities investigation for details). A revised method [redacted] was amended in 7/20/98. Method validation package has not been processed.

F. LABELING **Pending**

Per FDA request (7/9/98 facsimile memo), the proposed proprietary name and established name NORVIR[R] [redacted], have been revised to FDA's recommendation: NORVIR[R] (ritonavir capsules) soft gelatin. The chemistry section of the package insert has not been reviewed.

G. ESTABLISHMENT INSPECTION **Acceptable**

CGMP compliance status for Abbott Spa, Italy (DS manufacturer), Abbott North Chicago (DS manufacturer). [redacted]), and Abbott Park (DP packager, labeler, and release tester) was found acceptable on June 19, 1998.

CONCLUSIONS/RECOMMENDATIONS:

In conclusion, the chemistry section for this NDA is not approvable. Details of specific chemistry deficiencies and the data sets required for a resubmission are summarized in the draft NA letter.

Ko-Yu Lo, Ph.D., Review Chemist

Concurrence:
HFD-530/SMiller

cc:

Orig. NDA 20-945	HFD-530/KLo	
HFD-530/Div. File	HFD-530/MO	HFD-530/CSO
HFD-530/SMiller	HFD-830/CChen	

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/s/

Ko-yu Lo
3/1/04 04:54:08 PM
CHEMIST

Stephen Paul Miller
3/1/04 05:17:15 PM
CHEMIST

CDER Establishment Evaluation Report for June 29, 1998

Application: **NDA 20945/000**
Priority: **S**
Org Code: **530**
Stamp: **24-NOV-1997** Regulatory Due: **24-NOV-1998**
Action Goal:
District Goal: **15-MAY-1998**
Applicant: **ABBOTT LABS**
DEPT 491 AP6B 1
ABBOTT PARK, IL 60064
Brand Name: **NORVIR(RETONAVIR)SEC CAPS 100/200MG**
Established Name:
Generic Name: **RITONAVIR**
Dosage Form: **CAP (CAPSULE)**
Strength: **100&200 MG SOFT GEL CAP**

FDA Contacts:

D. GUMP	**(HFD-530)**	**301-827-2335**	**, Project Manager**
K. LO	**(HFD-530)**	**301-827-2397**	**, Review Chemist**
S. MILLER	**(HFD-530)**	**301-827-2392**	**, Team Leader**

Overall Recommendation:

ACCEPTABLE on 19-JUN-1998 by M. EGAS (HFD-322) 301-594-0095

Establishment: **1411365**
ABBOTT LABORATORIES
1401 14TH & SHERIDAN ROAD
NORTH CHICAGO, IL 60064
DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **01-MAY-1998**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**
Responsibilities: **DRUG SUBSTANCE MANUFACTURER**

Establishment: **1415939**
ABBOTT LABORATORIES
100 ABBOTT PARK RD
ABBOTT PARK, IL 60064
DMF No: **3023**
AADA No:

Profile: **CSG** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **01-MAY-1998**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**
Responsibilities: **FINISHED DOSAGE LABELER**
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER

Establishment: **9611151**
ABBOTT SPA
VIA PONTINA, KM 52-04010
CAMPOVERDE, , IT
DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **19-JUN-1998**
Responsibilities: **DRUG SUBSTANCE MANUFACTURER**

Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Establishment: [redacted]

DMF No: [redacted]
AADA No:

Profile: **CSG** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **11-MAY-1998**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: [redacted]
