CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-929

ADMINISTRATIVE DOCUMENTS

Time Sensitive Patent Information

pursuant to 21 C.F.R. § 314.53

for

NDA 20-929

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

Trade Name:	PULMICORT RESPULES™
Active Ingredient(s):	Budesonide
Strength(s):	0.25 mg/mL; 0.50 mg/mL;
Dosage Form:	Inhalation Suspension

A. This section should be completed for each individual patent

U.S. Patent Number: 4,787,536

Expiration Date: February 27, 2006

Type of Patent--Indicate all that apply:

1. Drug Substance (Active Ingredient) _Y _N
2. Drug Product (Composition/Formulation) x Y _N
3. Method of Use _Y _N

a. If patent claims method(s) of use, please specify approved method(s) of use or method(s) of use for which approval is being sought that are covered by patent:_____

Name of Patent Owner: Aktiebolaget Draco

U.S. Agent (if patent owner or applicant does not reside or have place of business in the US): Astra USA, Inc.

B. The following declaration statement is required if any of the above listed patents have Composition/Formulation or Method of Use claims.

The undersigned declares that the above stated United States Patent Number 4,787,536 covers the formulation of PULMICORT RESPULES™. This product is:

_ currently approved under section 505 of the Federal Food, Drug and Cosmetic Act.

OR

x the subject of this application for which approval is being sought.

Signed:
Date: 11/17/07
Title: Vice President of Regulatory Affairs
Telephone Number: (508) 366-1100, ext. 4739

AUG - 4 2000

EXCLUSIVITY SUMMARY for NDA # __20-929_____ SUPPL #_____

Trade Name __Pulmicort Respules___ Generic Name __budesonide inhalation suspension

Applicant Name ___AstraZeneca_____ HFD-570____

Approval Date, if known _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

   a) Is it an original NDA?

   YES /_X_/ NO /___/

   b) Is it an effectiveness supplement?

   YES /___/ NO /_X_/

   If yes, what type? (SE1, SE2, etc.) _____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

   YES /_X_/ NO /___/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   _____

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical

data:

_____

d) Did the applicant request exclusivity?

YES /___/ NO /_X_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx-to-OTC switches should be answered NO-please indicate as such.)

YES /___/ NO /_X_/

If yes, NDA #_____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this

particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_X_/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _20-233_____ _Rhinocort Nasal Spray

NDA# __20-441_____ __Pulmicort Turbuhaler

NDA# __20-746_____ ___Rhinocort Aqua Nasal Spray

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X_/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

_____

YES /___/ NO /___/

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /_X_/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X_/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

3072, 3069, and 3100

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "n[redacted] to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /_X_/
Investigation #2	YES /___/	NO /_X/
Investigation #3	YES /___/	NO /_X/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES /___/	NO /_X_/
Investigation #2	YES /___/	NO /_X_/
Investigation #3	YES /___/	NO /_X_/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

__3072_____ ____3069_____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	
IND # 44,535 YES /_X_/	NO /___/ Explain: _____
	_____
Investigation #2	
IND # 44,535 YES /_X/	NO /___/ Explain: _____
	_____
Investigation #3	
IND # 44,535 YES /_X/	NO /___/ Explain: _____
	_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

Investigation #2	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

APPEARS THIS WAY
ON ORIGINAL

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X__/

If yes, explain: _____

_____

/S/ 8/4/00

Signature Date

Title: Project Manager

/S/ 8/4/00

Signature Division Director Date

cc: Original NDA Division File HFD-93 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA Number:	020929	**Trade Name:**	PULMICORT RESPULES(BUDESONIDE) /0.25
Supplement Number:	000	**Generic Name:**	BUDESONIDE
Supplement Type:	N	**Dosage Form:**	
Regulatory Action:	PN	**COMIS Indication:**	MAINTENANCE TREATMENT OF ASTHMA AND PROPHYLACTIC THERAPY IN CHILDREN AGED TO 8 YEARS
Action Date:	2/10/00		

Indication # 1 Maintenance treatment of asthma and as prophylactic therapy in children 12 months to 8 years of age

Label Adequacy: Adequate for SOME pediatric age groups

Forumulation Needed: NEW FORMULATION developed with this submission

Comments (if any): August 4, 2000. Data only supported labeling down to 12 months.

Lower Range	Upper Range	Status	Date
12 months	8 years	Completed	

This page was completed based on information from Gretchen Trout

LS I — Signature - Gretchen Trout

8-4-00 — Date

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	20929	**Trade Name:**	PULMICORT RESPULES(BUDESONIDE) — /0.25
Supplement Number:		**Generic Name:**	BUDESONIDE
Supplement Type:		**Dosage Form:**	Suspension; Oral
Regulatory Action:	AE	**Proposed Indication:**	Maintenance treatment of asthma and as prophylactic therapy in children aged 12 months to 8 years.

IS THERE PEDIATRIC CONTENT IN THIS SUBMISSION? YES

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days)

____Children (25 Months-12 years)

____Infants (1-24 Months)

____Adolescents (13-16 Years)

_X_ Other Age Groups (listed): 12 months - 8 years

Label Status	ADEQUATE Labeling for ALL PEDIATRIC ages
Formulation Status	NO NEW FORMULATION is needed
Studies Needed	No further STUDIES are needed
Study Status	

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:
Dosage form is suspension for oral inhalation.

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, GRETCHEN TROUT

151 2/4/99

Signature Date

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

NDA/BLA # 20-929 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD 570 Trade and generic names/dosage form: (Budesonide Nebulizing Suspension) Pulmicort Respules Action: AP (AE) NA

Applicant Astra Therapeutic Class 3P

Indication(s) previously approved see attachment

Pediatric information in labeling of approved indication(s) is adequate X inadequate __

Proposed indication in this application maintenance treatment of asthma + prophylactic therapy for children — 8yr.

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? X Yes (Continue with questions) __ No (Sign and return the form)

WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)

— Neonates (Birth-1month) X Infants (1month-2yrs) X Children (2-12yrs) __ Adolecents(12-16yrs)

__ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

__ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

__ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

__ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

__ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

__ c. The applicant has committed to doing such studies as will be required.

__ (1) Studies are ongoing,

__ (2) Protocols were submitted and approved.

__ (3) Protocols were submitted and are under review.

__ (4) If no protocol has been submitted, attach memo describing status of discussions.

__ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

__ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

X 5. **If none of the above apply, attach an explanation, as necessary.**

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? __ Yes __ No

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from team leader (e.g., medical review, medical officer, team leader)

CS 1 _____ May 11, 1998

Signature of Preparer and Title Date

cc: Orig NDA/BLA # 20929
HFD-570 /Div File
NDA/BLA Action Package
HFD-006/ KRoberts

(revised 10/20/97)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, KHYATI ROBERTS, HFD-6 (ROBERTSK)

Budesonide is currently approved (in the form of a dry powder, as Pulmicort Turbuhaler) for the maintenance treatment of asthma and as prophylactic therapy in adults and pediatric patients six years of age or older. The proposed indication for this application is for the maintenance treatment of asthma and as prophylactic therapy in children aged [redacted] to 8 years.

ASTRA®
Astra USA

Debarment Certification

This certifies that Astra USA, Inc. has not used in any capacity any person identified by the United States Food and Drug Administration on the recent Debarment List.

Further, we certify that Astra USA, Inc. will not use the services in any capacity of anyone debarred by the United States Food and Drug Administration.

The following is a list of all relevant convictions (for which a person can be debarred) as described in section 306 (a) and (b). The list covers the past five (5) years for persons employed and/or affiliated with Astra USA, Inc. (including contractors) and responsible for the development of data and information to support approval of NDA 20-929 for Pulmicort Respules™ (budesonide nebulizing suspension).

Person	Date of Conviction	Charge
None	None	None

Dennis J. Bucceri
Vice President
Regulatory Affairs

11/17/97
Date

MAILING ADDRESS:
Astra USA, Inc.
P.O. Box 4500
Westborough, MA 01581-4500

OFFICE:
50 Otis Street
Westborough, MA

TEL:
508 366-1100

FAX:
508 366-7406
TELEX:
6810105-Cable/Astrapharm

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 20-929 Drug Pulmicort Respules Applicant AstraZeneca

RPM Trout Phone 7-1058

X 505(b)(1)
☐ 505(b)(2) Reference listed drug

☐ Fast Track ☐ Rolling Review Review priority: ☐ S X P

Pivotal IND(s) 44,535

Application classifications:
Chem Class 3
Other (e.g., orphan, OTC)

PDUFA Goal Dates:
Primary August 10, 2000
Secondary August 10, 2000

Arrange package in the following order:

Indicate N/A (not applicable), X (completed), or add a comment.

GENERAL INFORMATION:

- User Fee Information: X User Fee Paid
  ☐ User Fee Waiver (attach waiver notification letter)
  ☐ User Fee Exemption

- Action Letter..... X AP ☐ AE ☐ NA

- Labeling & Labels
  - FDA revised labeling and reviews..... See telecons 8/3-8/5
  - Original proposed labeling (package insert, patient package insert) ..... X dated 8/4/00
  - Other labeling in class (most recent 3) or class labeling..... X
  - Has DDMAC reviewed the labeling? ..... ☐ Yes (include review) ☐ No
  - Immediate container and carton labels ..... X dated 8/3/00
  - Nomenclature review X

- Application Integrity Policy (AIP) ☐ Applicant is on the AIP. This application ☐ is X is not on the AIP.
  - Exception for review (Center Director's memo)..... _____
  - OC Clearance for approval..... _____

Continued ⇨

- Status of advertising (if AP action) ☐ Reviewed (for Subpart H – attach review) — X Materials requested in AP letter

- Post-marketing Commitments — X
  - Agency request for Phase 4 Commitments — X see fax dated 8/3
  - Copy of Applicant's commitments — X

- Was Press Office notified of action (for approval action only)? — X Yes ☐ No
  - Copy of Press Release or Talk Paper — Notified 8/4/00 working on Talk Paper

- Patent
  - Information [505(b)(1)] — X
  - Patent Certification [505(b)(2)] — N/A
  - Copy of notification to patent holder [21 CFR 314.50 (i)(4)] — N/A

- Exclusivity Summary — X

- Debarment Statement — X

- Financial Disclosure
  - No disclosable information — N/A
  - Disclosable information – indicate where review is located — N/A

- Correspondence/Memoranda/Faxes — X

- Minutes of Meetings — X
  - Date of EOP2 Meeting _____
  - Date of pre NDA Meeting 9/16/96, 11/20/96, 12/6/96
  - Date of pre-AP Safety Conference _____

- Advisory Committee Meeting — N/A
  - Date of Meeting _____
  - Questions considered by the committee _____
  - Minutes or 48-hour alert or pertinent section of transcript _____

- Federal Register Notices, DESI documents — N/A

CLINICAL INFORMATION: — **Indicate N/A (not applicable), X (completed), or add a comment.**

- Summary memoranda (e.g., Office Director's memo, Division Director's memo, Group Leader's memo) — X

Continued ⇨

- ◆ Clinical review(s) and memoranda X
- ◆ Safety Update review(s) X
- ◆ Pediatric Information
  - ☐ Waiver/partial waiver (Indicate location of rationale for waiver) X Deferred
  - Pediatric Page..... X
  - ☐ Pediatric Exclusivity requested? ☐ Denied ☐ Granted ☐ Not Applicable
- ◆ Statistical review(s) and memoranda X
- ◆ Biopharmaceutical review(s) and memoranda..... X
- ◆ Abuse Liability review(s) ..... N/A
  - Recommendation for scheduling .....
- ◆ Microbiology (efficacy) review(s) and memoranda X
- ◆ DSI Audits X
  - X Clinical studies ☐ bioequivalence studies .....

CMC INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- ◆ CMC review(s) and memoranda ..... ✓
- ◆ Statistics review(s) and memoranda regarding dissolution and/or stability .....
- ◆ DMF review(s) .....
- ◆ Environmental Assessment review/FONSI/Categorical exemption ..... ✓
- ◆ Micro (validation of sterilization) review(s) and memoranda .....
- ◆ Facilities Inspection (include EES report)
  - Date completed _____ ..... X Acceptable ☐ Not Acceptable
- ◆ Methods Validation ..... ☐ Completed X Not Completed

PRECLINICAL PHARM/TOX INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- ◆ Pharm/Tox review(s) and memoranda X

Continued ⇨

- Memo from DSI regarding GLP inspection (if any) X

APPEARS THIS WAY
ON ORIGINAL

Continued ⇨

- Statistical review(s) of carcinogenicity studies ..... _____
- CAC/ECAC report ..... N/A

3 Page(s) Withheld

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: NDA 20929/000
Priority: 3P
Org Code: 570
Stamp: 20-NOV-1997 Regulatory Due: 10-AUG-2000
Action Goal:
District Goal: 15-MAR-1998
Applicant: ASTRA PHARMS
725 CHESTERBROOK BLVD
WAYNE, PA 190875677
Brand Name: PULMICORT RESPULES(BUDESONIDE) [redacted] /0.25
Established Name:
Generic Name: BUDESONIDE
Dosage Form: SUS (SUSPENSION)
Strength: 0.25; 0.5; [redacted] /2ML

FDA Contacts:
G. TROUT (HFD-570) 301-827-1050 , Project Manager
C. KIM (HFD-570) 301-827-1050 , Review Chemist
G. POOCHIKIAN (HFD-570) 301-827-1050 , Team Leader

Overall Recommendation:

ACCEPTABLE on 03-AUG-2000 by M. EGAS (HFD-322) 301-594-0095
WITHHOLD on 24-JUL-2000 by M. EGAS (HFD-322) 301-594-0095
ACCEPTABLE on 18-JUL-2000 by M. EGAS (HFD-322) 301-594-0095
ACCEPTABLE on 10-FEB-1999 by J. D AMBROGIO (HFD-324) 301-827-0062
ACCEPTABLE on 30-APR-1998 by M. EGAS (HFD-322) 301-594-0095

Establishment: 9610565
ASTRA PRODUCTION CHEMICALS A
SODERTALJE, , SW
DMF No:
AADA No:

Profile: CSN
OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 18-JUL-2000
Decision: ACCEPTABLE
Reason: BASED ON FILE REVIEW

Responsibilities:
DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE MICRONIZER
DRUG SUBSTANCE STABILITY TESTER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE STABILITY TESTER

Establishment: 1220331
ASTRA USA INC
50 OTIS ST
WESTBOROUGH, MA 015814500
DMF No:
AADA No:

Profile: LIQ
OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 16-FEB-2000
Decision: ACCEPTABLE
Reason: BASED ON FILE REVIEW
BASED ON PROFILE

Responsibilities:
FINISHED DOSAGE LABELER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment: [redacted]

DMF No: [redacted]
AADA No:

Profile: CSN
OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 22-FEB-2000
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: [redacted]

Establishment: [redacted]

DMF No:
AADA No:

Profile: CTL
OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 16-FEB-2000
Decision: ACCEPTABLE
Reason: BASED ON FILE REVIEW
BASED ON PROFILE

Responsibilities: [redacted]

Establishment: [redacted]

DMF No: [redacted]
AADA No:

Profile: CRU
OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 16-FEB-2000
Decision: ACCEPTABLE
Reason: BASED ON FILE REVIEW
BASED ON PROFILE

Responsibilities: [redacted]

Establishment: [redacted]

DMF No:
AADA No:

Profile: CRU
OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 03-AUG-2000
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: [redacted]

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Establishment: [redacted]

DMF No:
AADA No:

Profile: CSN OAI Status: NONE Responsibilities: [redacted]
Last Milestone: OC RECOMMENDATION
Milestone Date: 22-FEB-2000
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Establishment: [redacted]

DMF No:
AADA No:

Profile: CTL OAI Status: NONE Responsibilities: [redacted]
Last Milestone: OC RECOMMENDATION
Milestone Date: 16-FEB-2000
Decision: ACCEPTABLE
Reason: BASED ON FILE REVIEW

APPEARS THIS WAY
ON ORIGINAL

CDER Establishment Evaluation Report for September 04, 1998

Application: NDA 20929/000
Priority: 3P
Org Code: 570
Stamp: 20-NOV-1997 Regulatory Due: 20-MAY-1998
Action Goal:
District Goal: 15-MAR-1998
Applicant: ASTRA USA
50 OTIS ST
WESTBOROUGH, MA 015814500
Brand Name: PULMICORT RESPULES(BUDESONIDE [redacted] 0.25
Established Name:
Generic Name: BUDESONIDE
Dosage Form: SUS (SUSPENSION)
Strength: 0.25; 0.5; [redacted] 2ML

FDA Contacts:

G. TROUT	(HFD-570)	301-827-1050	, Project Manager
C. KIM	(HFD-570)	301-827-1050	, Review Chemist
G. POOCHIKIAN	(HFD-570)	301-827-1050	, Team Leader

Overall Recommendation:

ACCEPTABLE on 30-APR-1998 by M. EGAS (HFD-322) 301-594-0095

Establishment: 9610565
ASTRA PRODUCTION CHEMICALS
STRANGNASVAGEN 20
SODERTALJE, , SW
DMF No:
AADA No:

Profile: CSN
OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 30-APR-1998
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities:
- DRUG SUBSTANCE MANUFACTURER
- DRUG SUBSTANCE MICRONIZER
- DRUG SUBSTANCE STABILITY TESTER
- FINISHED DOSAGE MANUFACTURER
- FINISHED DOSAGE STABILITY TESTER

Establishment: 1220331
ASTRA USA INC
50 OTIS ST
WESTBOROUGH, MA 015814500
DMF No:
AADA No:

Profile: LIQ
OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 03-APR-1998
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities:
- FINISHED DOSAGE LABELER
- FINISHED DOSAGE MANUFACTURER
- FINISHED DOSAGE PACKAGER
- FINISHED DOSAGE RELEASE TESTER
- FINISHED DOSAGE STABILITY TESTER -

Establishment: [redacted]
DMF No: [redacted]
AADA No:

for September 04, 1998

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **14-JAN-1998**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities:

Establishment:

DMF No:
AADA No:

Profile: **CRU** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **14-JAN-1998**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities:

Establishment:

DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **14-JAN-1998**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities:

Establishment:

DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **14-JAN-1998**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities:

Establishment:

DMF No:

AADA No:

Profile: **CTL** OAI Status: **NONE** Responsibilities:
Last Milestone: **OC RECOMMENDATION**
Milestone Date **11-MAR-1998**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

for May 05, 1998

Application: NDA 20929/000 Priority: 3P Org Code: 570
Stamp: 20-NOV-1997 Regulatory Due: 20-MAY-1998 Action Goal: District Goal: 15-MAR-1998
Applicant: ASTRA USA Brand Name: PULMICORT RESPULES(BUDESONIDE) —— 0.25
Established Name:
Generic Name: BUDESONIDE
Dosage Form: SUS (SUSPENSION)
Strength: 0.25; 0.5; —— 2ML

FDA Contacts: G. TROUT (HFD-570) 301-827-1050 , Project Manager
C. KIM (HFD-570) 301-827-1050 , Review Chemist
G. POOCHIKIAN (HFD-570) 301-827-1050 , Team Leader

Overall Recommendation:

ACCEPTABLE on 30-APR-1998 by M. EGAS (HFD-322) 301-594-0095

Establishment: 9610565
ASTRA PRODUCTION CHEMICALS
STRANGNASVAGEN 20
SODERTALJE, , SW
DMF No:
AADA No:

Profile: CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 30-APR-1998
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE MICRONIZER
DRUG SUBSTANCE STABILITY TESTER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE STABILITY TESTER

Establishment: 1220331
ASTRA USA INC
50 OTIS ST
WESTBOROUGH, MA 015814500
DMF No:
AADA No:

Profile: LIQ OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 03-APR-1998
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: FINISHED DOSAGE LABELER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Establishment: ——
DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **11-MAR-1998**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**
Responsibilities: [redacted]

Establishment: **9610343** [redacted]
DMF No: [redacted]
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **14-JAN-1998**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**
Responsibilities: [redacted]

Establishment: [redacted]
DMF No: [redacted]
AADA No:

Profile: **CRU** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **14-JAN-1998**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**
Responsibilities: [redacted]

Establishment: [redacted]
DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **14-JAN-1998**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**
Responsibilities: [redacted]

Establishment: [redacted]
DMF No:

for May 05, 1998

AADA No:

Profile: CSN OAI Status: NONE Responsibilities:
Last Milestone: OC RECOMMENDATION
Milestone Date 14-JAN-1998
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

cc: Orig NDA 20-929
HFD-510/DIV.
HFD-570/Kim, Trent

1 Page(s) Withheld

PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

/S/ 5/19/98

TO (*Division Office*)	FROM:
Supervisory Microbiologist, HFD-805	Chong-Ho Kim, Ph.D., chemist, HFD-570

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
May 19, 1998		20-929	BC (Response to IR letter of April 21, 1998)	May 12, 1998

/S/ 5/19/98

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Pulmicort Respules (Budesonide nebulizing suspension)	1	P	July 20, 1998

NAME OF FIRM
Astra USA

REASON FOR REQUEST

I. GENERAL

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

II. BIOMETRICS

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

III. BIOPHARMACEUTICS

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

IV. DRUG EXPERIENCE

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

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS (*Attach additional sheets if necessary*)
Please review the applicant's response to our microbiology comments which was faxed to them on April 21, 1998 (Dr. Neal Sweeney's review).

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (*Check one*)
/S/	☐ MAIL (X) HAND
SIGNATURE OF RECE /S/	SIGNATURE OF DELIVERER /S/

RM FDA 3291 (7/83)

cc: NDA 20-929 File; HFD-570/Div. File; HFD-570/Ckim; HFD-570/GTrout, Schwartz

SK 5/20/98

PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			**REQUEST FOR CONSULTATION**	
TO (*Division Office*) Supervisory Microbiologist, HFD-160			FROM: Chong-Ho Kim, Ph.D., chemist, HFD-570	1S/ 12/11/97
ATE December 11, 1997	IND NO.	NDA NO. 20-929	TYPE OF DOCUMENT new	DATE OF DOCUMENT November 18, 1997
NAME OF DRUG Pulmicort Respules (Budesonide nebulizing suspension)		PRIORITY CONSIDERATION 1	CLASSIFICATION OF DRUG P	DESIRED COMPLETION DATE January 15, 1997
NAME OF FIRM Astra USA				

REASON FOR REQUEST

1. GENERAL

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

II. BIOMETRICS

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

.ıI. BIOPHARMACEUTICS

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

IV. DRUG EXPERIENCE

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

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS (*Attach additional sheets if necessary*) See Volume 1.5
Please review the microbiology section of the referenced NDA; the applicant is using a _____ . of the drug substance followed by _____ manufacturing of the drug product. The NDA was filed as "1P" drug which does not give us much time to review.

SIGNATURE OF REQUESTER /S/	METHOD OF DELIVERY (*Check one*) ☐ MAIL (X) HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

)RM FDA 3291 (7/83)

cc: NDA 20-929 File; HFD-570/Div. File; HFD-570/Ckim; HFD-570/GTrout

13 Page(s) Withheld

Director's Memorandum

Memorandum to:	NDA 20-929
Product:	Budesonide nebulizing suspension (Pulmicort Respules)
Memo date:	8-4-00
Memo from:	Robert J. Meyer, MD Director, DPADP

ADMINISTRATIVE

THIS MEMORANDUM IS TO DOCUMENT THE DECISIONAL CONCLUSIONS FOR NDA 20-929 - BUDESONIDE (PULMICORT) NEBULIZING SUSPENSION, THE FIRST CORTICOSTEROID NEBULIZING-SUSPENSION FOR TREATMENT OF ASTHMA. THIS APPLICATION WAS FIRST SUBMITTED IN NOV. 18, 1997 AND GIVEN A PRIORITY REVIEW. ITS ORIGINAL PROPOSED INDICATION WAS SPECIFIC [redacted] FOR CHILDREN WITH ASTHMA AND THE PROPOSED AGE RANGE FOR TREATMENT IS [redacted] TO 8 YEARS. THE NDA WAS GIVEN AN APPROVABLE ACTION DUE TO SERIOUS CMC DEFICIENCIES IN 1998. ADDITIONALLY, AS A RESULT OF THE CLINICAL REVIEW, THE SPONSOR WAS TOLD THAT [redacted] PLEASE SEE ORIGINAL MEMOS – INCLUDING DR. JENKINS' DIVISION DIRECTOR MEMO FOR DETAILS ON THIS DECISION.

THE SPONSOR RESUBMITTED IN AUGUST 1998, AMENDING THE PROPOSED INDICATIONS TO 1 YEAR OF AGE AS THE LOWER BOUND, AND [redacted] THIS RESUBMISSION WAS ALSO NOT APPROVABLE DUE TO CMC CONCERNS. [redacted] THIS LED TO EXTENSIVE TESTING AND A REDESIGN OF THE [redacted] RESPULE, WHICH HAS APPARENTLY ELIMINATED THIS EFFECT.

THE SPONSOR RESUBMITTED ON FEB. 9TH, 2000. THIS SUBMISSION LARGELY IS COMPRISED ON LABELING AND CMC INFORMATION, AS NO NEW STUDIES HAD BEEN PROPOSED OR REQUIRED.

CMC:

THE SPONSOR HAS ADEQUATELY ADDRESSED MOST CMC CONCERNS, INCLUDING THE PREVIOUSLY IDENTIFIED [redacted] WHILE THE SPONSOR HAS PROVIDED REASONABLE DATA ON THE [redacted] CONTAINED IN THE [redacted] (I.E., FOIL, [redacted] RESPULE), THEY HAVE NOT YET CHARACTERIZED AND SET SPECIFICATIONS FOR [redacted] IN THE FORMULATION. ORDINARILY, THIS WOULD BE EXPECTED PRIOR TO APPROVAL. HOWEVER, DUE TO THE [redacted] AND DUE TO THE IMPORTANCE OF THIS PRODUCT, WE WILL BE ACCEPTING A PHASE 4 COMMITMENT TO COMPLETE THE ONGOING [redacted] BY OCTOBER 12TH, 2000 SO THAT THIS PRODUCT MAY BE APPROVED THIS CYCLE.

CLINICAL:

SEE DR. PURUCKER'S LABELING REVIEW / SAFETY UPDATE. ESSENTIALLY, THE PROPOSED LABEL AS RESUBMITTED WAS ACCEPTABLE DUE TO PREVIOUS LABELING COMMENTS SENT TO THE SPONSOR, SAVE FOR SOME DETAILS AND WORDING. WE HAVE ACHIEVED FINAL, ACCEPTABLE

LANGUAGE AND CONTENT. THE SAFETY UPDATE (A REPORTING OF SAFETY RESULTS FROM CLINICAL TRIALS AND THE SRS DATABASE IN THE INTERIM) DID NOT IDENTIFY ANY ISSUES THAT IMPACT ON APPROVAL OR LABELING.

THE DIVISION IS REQUESTING A CLINICAL PHASE 4 COMMITMENT. SINCE THIS IS THE FIRST INHALED CORTICOSTEROID PRODUCT PROPOSED DOWN TO AN AGE WHERE PRIMARY VACCINATION SERIES WILL BE GIVEN, THE DIVISION HAS OBTAINED A COMMITMENT FROM THE SPONSOR TO STUDY THE EFFECTS OF PULMICORT RESPULES TREATMENT ON THE IMMUNE-RESPONSE TO A LIVE VIRUS VACCINE (SUCH AS VARICELLA – WHICH IS GIVEN AT AROUND 1.5 YEARS OF AGE). THE DIVISION'S CONCERN IS THAT THE INHALED STEROID MAY ALTER THE ROBUSTNESS OF THE IMMUNE RESPONSE TO SUCH VACCINATIONS, AND THEREFORE WOULD LIKE CONTROLLED DATA TO AT LEAST BEGIN TO ADDRESS THIS CONCERN. THE SPONSOR HAS COMMITTED TO PROVIDE THESE DATA BY OCT. 1, 2003.

RECOMMENDATION:
THIS PRODUCT WILL BE APPROVED BASED ON THE ORIGINAL NDA AND THE ADDITIONAL DATA PROVIDED THROUGH THE RESUBMISSIONS, INCLUDING THE RESUBMISSION OF 2/10/00.

/S/

ROBERT J. MEYER, MD
DIRECTOR, DIVISION OF PULMONARY AND ALLERGY DRUG PRODUCTS

CC: Purucker/Medical Team Leader/HFD-570
Trout/project manager/HFD-570
Division File/HFD-570
NDA #20-929

Trust

MEMORANDUM

DATE: May 20, 1998

TO: NDA 20-929

FROM: John K. Jenkins, M.D.
Director, Division of Pulmonary Drug Products, HFD-570

SUBJECT: Overview of NDA Review Issues

Administrative

NDA 20-929 for Pulmicort Respules (budesonide inhalation suspension, also abbreviated in this memo as BNS for "budesonide nebulizing suspension") was originally submitted by Astra USA on November 20, 1997. Due to the unique nature of the proposed indication; i.e., the first inhaled corticosteroid for use in children as young as [redacted] of age, the Division determined that the application would receive a priority review ("P" drug). The Division made plans to present the NDA for review at a meeting of the Pulmonary and Allergy Drugs Advisory Committee (PADAC) in April, however, that meeting was postponed when it became clear that the Committee members and consultants available for the proposed meeting date would not include any pediatric pulmonologists or allergists. It was felt that this lack of pediatric expertise would not provide the sponsor or the Agency with the level of expert review and advice that was appropriate for this product. Furthermore, it had become clear that there were significant CMC deficiencies with the application that could not be resolved within the first review cycle. It is anticipated that the NDA will be submitted for review by the PADAC once the NDA is resubmitted in response to the first action letter. The sponsor received a CMC information request letter on April 15, 1998, listing the CMC deficiencies as specified under the FDA Modernization Act of 1997 (FDAMA). The current user fee goal date for NDA 20-929 is May 20, 1998.

Clinical

This application represents the first corticosteroid formulated as a suspension for nebulization submitted for review in the U.S. The application is also unique in that the sponsor is proposing that the product be specifically indicated only for children between the ages of [redacted] and 8 years and not for older children or adults. As primary support of the proposed indication, the sponsor submitted the results of three 12-week, randomized, double-blind, placebo-controlled, parallel-group U.S. clinical trials (04-3069, 04-3072, and 04-3100) in pediatric asthma patients aged 6 months to 8 years and one open-label, long-term U.S. trial (04-3069B) which included patients treated with Pulmicort Respules for up to 52 weeks. Please refer to the Medical Officer Review prepared by Dr. Chu and to the Medical Team Leader Memorandum prepared by Dr. Meyer for a more detailed review of the clinical section of this NDA.

In trial 04-3100 in patients aged 7 months to 8 years, BNS at doses of 0.25 and 0.5 mg twice

daily and 1.0 mg once daily was demonstrated to be statistically significantly different from placebo (after adjustments for multiple comparisons) for both daytime and nighttime asthma symptom scores (with the exception of daytime scores for 1.0 mg once daily), the pre-specified primary endpoints. The 0.25 mg twice daily dose of BNS was only numerically superior to placebo. This pattern of findings also held true for most of the secondary efficacy variables; for some secondary endpoints the 0.25 mg once daily BNS dose was statistically different from placebo ($p < 0.05$). Overall, there was a suggestion that 0.5 mg twice daily was more efficacious than 1 mg once daily. The adverse event profile of BNS in this study was generally consistent with the types of events observed for other oral inhaled corticosteroids and the frequency of adverse event reporting was generally comparably to that observed in the placebo group with the possible exception of oral candidiasis. ACTH stimulation testing did not reveal a clear pattern of adverse impact of BNS on basal cortisol or adrenal reserve.

In trial 04-3069 in pediatric asthma patients aged 6 months to 8 years, BNS at doses of 0.25 and 0.5 mg once daily was demonstrated to be statistically significantly different from placebo (after adjustments for multiple comparisons) for nighttime asthma symptom scores; only 0.25 mg once daily was statistically significantly different from placebo (after adjustments for multiple comparisons) for daytime asthma symptom scores. All doses tested (0.25, 0.5, and 1.0 mg once daily) were different from placebo ($p < 0.05$) for both daytime and nighttime symptom scores prior to correction for multiple comparisons. Statistically significant differences from placebo were infrequently observed for any dose group for the secondary efficacy endpoints. The adverse event profile for BNS was generally consistent with that seen for other inhaled corticosteroids and generally comparable to that observed in the placebo group. ACTH stimulation testing did not reveal a clear pattern of adverse impact of BNS on basal cortisol or adrenal reserve.

In trial 04-3072 in pediatric asthma pateints aged 4 to 8 years, BNS at doses of 0.25, 0.5, and 1.0 mg twice daily was demonstrated to be statistically significantly different from placebo (after adjustments for multiple comparisons) for nighttime (except 0.5 mg twice daily) and daytime asthma symptom scores. A similar pattern for findings (without correction for multiple comparisons) was also noted for many of the secondary efficacy variables. Again, the adverse event profile for BNS was generally consistent with that seen for other inhaled corticosteroids and generally comparable to that observed in the placebo group except for rhinitis, coughing, oral candidiasis, and headache. Again, ACTH stimulation testing did not reveal a clear pattern of adverse impact of BNS on basal cortisol or adrenal reserve, however, there was a numerically larger decreased in stimulated cortisol in the 1.0 mg twice daily group than in placebo at the end of 12 weeks.

In trial 04-3069B which assessed the long-term safety of BNS versus conventional therapy, excluding inhaled corticosteroids, in patients 8 years and younger for up to 52-weeks, there was a suggestion of continued efficacy of BNS as assessed by the time to discontinuation of study treatment although for most of the pre-specified efficacy endpoints there were not significant differences between the groups (Note: this was an open-label study which limits data interpretation for efficacy). From a safety perspective, 14% of patients treated with BNS

who demonstrated normal responsiveness to ACTH at baseline demonstated an abnormal response at week 52; in contrast none of the conventional therapy patients demonstrated an abnormal response at week 52. This suggests that systemic effects are seen with BNS with long-term administration. This was further confirmed by the fact that the growth velocity of BNS-treated patients was statistically significantly lower than that observed in the conventional therapy group (-0.84 cm/year). The magnitude of the reduction in growth velocity was very comparable to that seen with other inhaled and intranasal corticosteroids at therapeutic doses in several recently completed studies.

One supportive non-U.S. study also warrants mentioning in this summary overview. Study 04-2213 was a double-blind, placebo-controlled, parallel-group study in pediatric patients (aged 9 months to 5 years) with severe asthma who were receiving oral corticosteroids at baseline. Thirty-seven patients were randomized to either 1.0 mg BNS twice daily or placebo for 8 weeks. The study demonstrated a statistically significant difference in oral corticosteroid reduction favoring the BNS group and in the number of patients that were able to be discontinue oral corticosteroids during the double-blind period. Importantly, no assessment of systemic effects of the high dose of BNS were conducted in this trial; i.e., it is not possible to assess whether the potential systemic corticosteroid effects of the high dose BNS were greater than, equal to, or less than that of the oral corticosteroid dose it is intended to replace (the mean baseline oral dose was 1.3 mg/kg).

In conclusion, I concur with Drs. Chu and Meyer that this application is approvable from a clinical standpoint, however, I also concur with the reviewers that there are several issues related to the proposed labeling claims by the sponsor that are not adequately supported by the currently available data. These issues include; 2) the data have not consistently supported efficacy of the once daily dosing regimens, the twice daily dosing regimens appear to be more consistently effective, and 3) The sponsor will be asked in the action letter to provide any additional data that they may have to address these issues.

The long-term safety study clearly demonstrated an effect of BNS on growth velocity, a finding that was much more evident than were alterations in adrenal function. This finding suggests that the dose-response curve for growth suppression for BNS may be quite different than the dose-response curve for effects on adrenal function as measured by basal and stimulated cortisol levels. A similar observation has been noted in several other recently completed clinical trials assessing the impact of other inhaled and intranasal corticosteroids on growth. While this finding does not preclude approval of the product for use in the target patient population, the data will need to be carefully reflected in the product labeling and clinicians

will need to be cautioned to ensure that they use the lowest effective dose of BNS in patients where its use is clinically warranted and that they carefully monitor the patients for any evidence of untoward systemic corticosteroid effects. The Division plans to present the recently emerging data on the impact of inhaled and intranasal corticosteroids to a joint meeting of the PADAC and Metabolic and Endocrine Drugs Advisory Committee on July 30 and 31, 1998. That discussion will focus on a comprehensive review of available data on growth for these products and a discussion of proposed class labeling language developed by the division. As noted earlier, the Pulmicort Respules NDA will also be presented to a future meeting of the PADAC for review. Based on the outcomes of these meetings, it is possible that additional significant changes to the labeling for BNS will be necessary.

Since the current action letter will not be an approval, the sponsor will be provided only general labeling comments from the clinical perspective.

Pre-clinical

Budesonide has been previously approved for marketing in the US for use by the intranasal (Rhinocort) and the oral inhaled route (Pulmicort Turbuhaler). In current application, the sponsor submitted three new inhalation toxicology studies designed to support the safety of BNS in patients as young as [redacted] of age (a 1-month study in immature rats aged 10 days at start, a 3-month study in immature dogs aged 41 days at start, and a 6-month inhalation study in rats of budesonide plus the excipients polysorbate 80 and potassium sorbate). Please refer to the preclinical review prepared by Dr. Vogel and the Pharmacology/Toxicology Team Leader Memorandum prepared by Dr. Sun for more detailed review of the preclinical findings relevant to this application. Overall, the newly submitted studies and the previously submitted studies adequately support the safety of BNS for use in children as young as [redacted]

There are no outstanding pharmacology/toxicology issues for this application other than the fact that the sponsor needs to submit the final study report for the 3-month inhalation toxicology study in immature dogs for review. The application is approvable from a preclinical standpoint pending submission of that final study report and acceptable labeling.

CMC

Pulmicort Respules are proposed for marketing in [redacted] dosage strengths (0.25 mg, 0.5 mg, [redacted], each in 2 mL [redacted] vials. It is important to note that this product is a suspension, not a solution like other approved products for use in nebulizers. As noted above, the sponsor received a detailed information request letter detailing CMC deficiencies in this application on April 15, 1998. To date the sponsor has not responded to this IR letter and these same deficiencies will be repeated in the action letter. A couple of the issues raised in the IR warrant mention in this memo. First, the sponsor has proposed that the labeling on the [redacted] vials themselves be in the form of an [redacted] as has been the case for all other [redacted] vials approved by this division. Given the fact that the [redacted] the division does not consider this approach to be optimal and will strongly suggest that the sponsor consider changing to [redacted]. If the sponsor chooses to stay with [redacted] it will be necessary for them to

submit detailed data in order to qualify the safety of the [redacted] and cause adverse events when administered to patients with hyperreactive airways). Another issue related to the [redacted] the fact that the [redacted] vials. Given the fact that the sponsor is proposing to market [redacted] different strengths of the product, this could result in medication errors and must be remedied prior to approval.

The application is not approvable from a CMC standpoint at this time.

Clinical Pharmacology and Biopharmaceutics

Please refer to the review prepared by Dr. Gillespie for a more detailed overview of the Clinical Pharmacology and Biopharmaceutics portion of this NDA. The sponsor conducted only limited pharmacokinetics studies of BNS in the target patient population. From the available data, it appears that the absolute bioavailablility of BNS delivered by a Pari LC Jet nebulizer in children is approximately 6% (based on nominal dose, approximately 26% when calculated based on delivered dose) as compared to approximately 16% in adults for BNS and approximately 38% in adults for Pulmicort Turbuhaler. This finding is not surprising given the known inefficiency of nebulizers.

There are no outstanding issues and the application is approvable from a clinical pharmacology and biopharmaceutics standpoint with acceptable labeling.

Data Verification

The Division of Scientific Investigations performed an audits of four clinical sites involved in the pivotal clinical trials for this application. All four sites were rated as NAI. Based on the results of the DSI audits, and based on the limited auditing of the NDA performed by the medical reviewer, there are no reasons to suspect any serious data integrity problems with the NDA database.

Labeling

The proposed trademark "Pulmicort Respules" has been found to be acceptable to the division and the CDER Labeling and Nomenclature Committee. Since the action will not be an approval and since the sponsor is being asked to submit additional data that may significantly impact on labeling, only preliminary labeling comments will be provided to the sponsor at this time.

Conclusion

There are numerous outstanding CMC deficiencies that must be adequately addressed prior to this application being approved. However, from the perspective of the other disciplines the application is approvable with acceptable labeling (even the identified clinical issues can be handled through labeling). Therefore, consistent with previous applications of the "approvable" letter in similar cases by the division and given the statutory mandate under FDAMA to phaseout the "approvable" letter and replace it with a "deficiency" letter, this application is APPROVABLE. The outstanding deficiencies will be listed in the action letter.

cc:
NDA 20-929
HFD-570 Division File
HFD-570/Jenkins
HFD-570/Trout
HFD-570/Meyer

MAY - 5 1998

Clinical Team Leader Review Memorandum

Memorandum to:	NDA 20-929 file
Product:	Budesonide nebulizing suspension
Memo date:	5-5-98
Memo from:	Robert J. Meyer, MD Medical Team Leader, DPDP

THIS MEMORANDUM IS TO DOCUMENT THE SECONDARY REVIEW CONCLUSIONS ON THE NDA FOR BUDESONIDE (PULMICORT) NEBULIZING SUSPENSION, THE FIRST CORTICOSTEROID NEBULIZING SUSPENSION FOR TREATMENT OF ASTHMA. THIS APPLICATION IS SPECIFICALLY FOR CHILDREN AND THE PROPOSED AGE RANGE FOR TREATMENT IS [redacted] TO 8 YEARS.

OVERVIEW:

BUDESONIDE WAS APPROVED FOR MARKETING IN A DRY POWDER FORMULATION (TURBUHALER) [redacted] JUNE OF 1997 FOR THE MAINTENANCE TREATMENT OF ASTHMA. THE APPROVED POPULATION IS ADULTS AND CHILDREN AGES 6 AND ABOVE, WITH A DOSE RANGE OF 200 µG BID TO 800 µG BID. ASTRA, THE DRUG'S SPONSOR, HAS DEVELOPED A SUSPENSION FOR NEBULIZATION (LATER REFERRED TO AS BNS), THE FIRST SUCH CORTICOSTEROID PRODUCT TO BE SUBMITTED FOR NDA REVIEW. THIS MEMO WILL BE SHORT, REFLECTING MAINLY SOME DETAILS OF THE SECONDARY REVIEW OPINION. SEE DR. SHAN CHU'S EXCELLENT MEDICAL OFFICER REVIEW FOR MORE DETAILS.

EFFICACY:

THE EFFICACY DATA FOR THIS NDA, IN MANY WAYS, STAND ALONE FROM THE PULMICORT TURBUHALER APPLICATION. THERE ARE RELATIVELY FEW DATA LINKING THE TWO, AND FROM THE CLINICAL STANDPOINT, THERE ARE SUFFICIENT DATA WITH BNS ALONE TO RENDER AN OPINION ON EFFICACY. THE SPONSOR SUBMITTED THREE MAIN "PIVOTAL" TRIALS - 04-3100, 04-3069 AND 04-3072. THESE TRIALS EXAMINED DOSES RANGING FROM 0.25 MG ONCE DAILY TO 1 MILLIGRAM TWICE DAILY, PRIMARILY ADMINISTERED TO CHILDREN EITHER PREVIOUSLY STEROID NAÏVE OR PRIOR USERS OF INHALED CORTICOSTEROIDS. BECAUSE THE AGE RANGE WENT DOWN TO 6 MONTHS (SEE NOTE BELOW) AND WAS CLEARLY BELOW THAT WHERE PFTS ARE RELIABLE, THE PRIMARY ENDPOINTS WERE AM AND PM SYMPTOM SCORES, WHERE THE SPONSOR PLANNED TO WIN ON BOTH. THIS WAS SUPPORTED BY TRADITIONAL SECONDARY ENDPOINTS, HOWEVER, INCLUDING PEAK FLOWS AND SPIROMETRY WHERE OBTAINABLE. THIS ENDPOINT CHOICE AND THE NEED TO 'WIN' ON BOTH ELEMENTS OF THE PRIMARY ANALYSIS WAS A SPECIFIC DISCUSSION OF THE END-OF-PHASE 2 MEETING. THE SPONSOR HAS SHOWN CONVINCING DATA FOR THE EFFICACY OF THE BID DOSING, WITH ONLY SOME NUMERICAL HINTS OF A DOSE RESPONSE OVER THE DOSE RANGE OF 0.25 TO 1.0 MG TWICE DAILY. IN FACT, STUDY 307 SHOWED NO SEPARATION EITHER STATISTICALLY NOR NUMERICALLY BETWEEN 1.0 MG BID AND 0.50 MG BID.

THE DATA SUPPORTING THE EFFICACY OF ONCE DAILY DOSING ARE NOT AS STRONG AS WITH BID. IN STUDY 3100 WHERE THE TWO DOSING INTERVALS WERE STUDIED HEAD-TO-HEAD, THERE IS A CLEAR SIGNAL THAT THE SAME DAILY DOSE ADMINISTERED TWICE DAILY IS MORE EFFECTIVE THAN ONCE DAILY, INCLUDING ON THE PRIMARY ENDPOINTS, PFTS, RESCUE MEDICATION USE AND DROP-OUTS FOR LACK OF EFFECT. IT SHOULD BE POINTED OUT THAT IN THE STUDY WHERE ONLY QD DOSING WAS EXAMINED, 3069, THERE WAS STATISTICAL SEPARATION FROM PLACEBO FOR EACH OF THE DOSES COMPARED TO PLACEBO ON BOTH THE PRIMARY ENDPOINTS. THIS DID NOT ALWAYS HOLD TRUE FOR ALL QD DOSES EXAMINED, HOWEVER.

SAFETY:

THE SAFETY DATA IN THIS NDA WERE REASONABLY EXTENSIVE, INCLUDING A LONG TERM SAFETY TRIAL WITH THE BNS VERSUS STANDARD CARE (USUALLY CROMOLYN SODIUM) IN AN OPEN-LABEL STUDY WHICH INCLUDED AMONGST THE SAFETY ENDPOINTS GROWTH AND HPA AXIS ASSESSMENTS. THE DOSE OF BNS IN THIS TRIAL STARTED AT 0.5 MG ONCE DAILY, BUT WAS TITRATED ACCORDING TO CLINICAL NEED BETWEEN 0 AND 1 MG QD. WHILE THIS WAS OPEN-LABEL TRIAL AND NOT PRIMARILY CONDUCTED FOR EFFICACY, IT DOES SUPPORT EFFICACY IN THAT THERE WERE FEWER DROP-OUTS FOR LACK OF EFFICACY IN THE BNS GROUP (MOST OTHER 'EFFICACY' VARIABLES SHOWED LITTLE DIFFERENCE BETWEEN THE GROUPS). MOST OF THE CONVENTIONAL SAFETY ENDPOINTS SHOWED A TYPICAL PROFILE FOR AN INHALED CORTICOSTEROID PRODUCT. HOWEVER, IN THE BNS GROUP, 14% WHO SHOWED NORMAL ACTH-STIMULATED CORTISOLS AT BASELINE BECAME ABNORMAL IN THE TRIAL, AS OPPOSED TO 0% IN CONVENTIONAL THERAPY. ALSO, ALTHOUGH THIS WAS NOT A RIGOROUSLY CONTROLLED GROWTH STUDY, THERE WAS A STATISTICALLY LOWER GROWTH IN BNS TREATED PATIENTS COMPARED TO CONVENTIONAL THERAPY (6.55 CM VS. 7.39 CM), WHICH WOULD BE IN KEEPING WITH DATA FROM OTHER CORTICOSTEROID GROWTH STUDIES WHICH SUGGEST GROWTH EFFECTS OCCUR AT LOWER SYSTEMIC LEVELS THAN THOSE NEEDED TO SUPPRESS HPA FUNCTION AS ASSESSED BY ACTH TESTING.

THE OTHER SAFETY DATA IN THIS NDA FROM THE PIVOTAL TRIALS, NON-US TRIALS AND POST-MARKETING EXPERIENCE DO NOT SUGGEST ANY UNIQUE TOXICITIES OF THIS AGENT, BEYOND THOSE THAT MIGHT BE EXPECTED WITH A CORTICOSTEROID.

OVERALL CONCLUSIONS:

I AM IN AGREEMENT WITH DR. CHU'S ASSESSMENT THAT THIS APPLICATION IS APPROVABLE FROM THE CLINICAL STANDPOINT. ALTHOUGH ADVISORY COMMITTEE INPUT IS PENDING AND MAY CHANGE SOME OF MY SPECIFIC CONCLUSIONS, I FEEL THE FOLLOWING NEEDS TO BE ADDRESSED IN LABELING:

- [redacted]
- [redacted]
- [redacted]
- THE GROWTH DATA SHOULD BE BETTER DISCUSSED IN THE LABELING THAN AS CURRENTLY CONTAINED IN THE PROPOSED LABEL SUBMITTED BY THE SPONSOR. IT SHOULD BE NOTED THAT DUE TO AN ERROR IN THE SPONSOR'S ANALYSIS AND REPORT OF THESE DATA IN NDA, THE ORIGINAL CONCLUSION THAT THERE WAS NO STATISTICAL SEPARATION ON THE GROWTH ENDPOINT WAS WRONG

[redacted]

RECOMMENDATION:

I RECOMMEND APPROVAL OF THIS PRODUCT, ONCE ALL CMC ISSUES AND LABELING ISSUES ARE RESOLVED. SINCE THE CMC IS STILL OUTSTANDING AND THIS ACTION WILL BE "APPROVABLE," OUR LABELING COMMENTS INCLUDED IN THE ACTION LETTER WILL STILL BE FAIRLY GENERAL. WHEN A FULL RESPONSE TO THIS ACTION LETTER IS OBTAINED FROM THE SPONSOR, A MEETING OF THE PULMONARY-ALLERGY DRUGS ADVISORY COMMITTEE SHOULD BE SCHEDULED TO REVIEW THE CLINICAL DATA OF THIS APPLICATION AND ADDRESS CONCERNS, INCLUDING THOSE ABOVE.

1st

ROBERT J. MEYER, MD 5/5/98
MEDICAL TEAM LEADER
DIVISION OF PULMONARY DRUG PRODUCTS

CC: Chu/Medical Officer/HFD-570
Meyer/Medical Team Leader/HFD-570
Trout/project manager/HFD-570
Division File/HFD-570
NDA #20-929

INTEROFFICE MEMO #2

TO: NDA 20929
FROM: C. Joseph Sun, Ph. D., Pharmacologist Team Leader
DATE: February 4, 1999

/S/
Feb. 4, 1999

The original interoffice memo of May 19, 1998 states that the completed 3-month study in dogs of 1-2 weeks of age should be reviewed to ensure that there were no unexpected findings.

Similar glucocorticoid effects and decreased lung weight were observed in treated dogs of 1-2 weeks of age to those reported in treated dogs of 5-6 weeks of age. The younger pups may have been slightly more sensitive to the older pups. There were no unexpected findings from the 3-month study in dogs of 1-2 weeks of age. Therefore, I concur with pharmacologist's conclusion that the 3-month study in dogs of 1-2 weeks does not raise special concerns for use of budesonide in infants (see pharmacology review #2 for an overall evaluation of pharmacology and toxicology data submitted on August 7, 1998). The drug is approvable from a preclinical standpoint.

There is no outstanding preclinical issue.

Orig. NDA
HFD-570/Division File
HFD-570/Sun
Hfd-570/Trout

INTEROFFICE MEMO

TO: NDA 20929
FROM: C. Joseph Sun, Ph. D., Team Leader Pharmacologist
DATE: May 19, 1998

/S/
- May 19, 1998

I concur with pharmacologist's recommendation that pharmacology and toxicology of budesonide have been adequately studied and the drug is approvable from a preclinical standpoint pending the results of the completed 3-month study in dogs of 1-2 weeks of age (see pharmacology review for an overall evaluation of pharmacology and toxicology data in this application).

Pharmacology: The anti-inflammatory actions of budesonide are typical for its class and did not distinguish it form other glucocorticoids. Its anti-inflammatory activity in rat ear [redacted] edema assay is proportional to glucocorticoid-receptor binding affinity. Inhaled or intratracheal budesonide also inhibited airway inflammation mediated by allergic challenge or other triggers in several animal models.

General toxicity: Chronic inhalation toxicity studies (up to 12 months) were conducted in rats and dogs. Typical systemic glucocorticoid effects were observed. Some effects in the respiratory tree (accumulation of alveolar macrophages, pulmonary perivascular lymphocyte infiltration and increased mucus production) were reported in rats. However, no local respiratory tract effects were observed in dogs. All of the toxicity observed after inhaled budesonide treatement in the immature rats (10 days of age) and dogs (5-6 weeks of age) were typical glucocorticoid calss effects except that decreased lung weight was seen in the immature dogs. The decreased lung weight in immature dogs was associated with nearly complete suppression of ACTH-stimulated cortisol responses. Young dogs may be more sensitive than human children to systemic glucocorticoid since human children were well tolerated this exposure (AUC) level. The age of dogs (41 days) at the start of the 3-month study probably corresponds to a 1 -1 ½ year old child. The completed study in a younger dogs (1-2 weeks of age) will be reviewed to ensure that there were no unexpected findings. A 6-month inhalation study in rats with inactive ingredients polysorbate 80 and potassium sorbate showed no effects on the respiratory tract attributable to the excipients. The study adequately bridges polysorbate 80 as an inactive ingredient for the current inhalation formulation to the well characterized profiles of oral polysorbate 80.

Reproductive toxicity: Budesonide was teratogenic and embryocidal in rabbits and rats by subcutaneous administration. However, it was not teratogenic or embryocidal in rats by inhalation administration. Thus, pregnancy category C is appropriate.

Genotoxicity: It was not mutagenic or clastogenic in Ames test, mouse micronucleus test, mouse lympoma test, chromosome aberration test in human lymphocytes, recessive lethal test in Drosophila melanogaster and DNA repair analysis in rat hepatocyte.

Carcinogencity: In three 2-year oral carcinogencity studies in rats, budesonide caused increases in the incidence of glioma in only one study and not reproducible in two subsequent studies or hepatocellular tumors in two other studies, typical finding of other reference steroids. No effects were reported in a 91-week oral carcinogenicity study in mice.

Labeling: Carcinogenesis, mutagenesis and impairment of fertility and pregnancy category C sections have been revised to incorporate the above-mentioned preclinical findings.

The completed 3-month study in dogs of 1-2 weeks of age should be reviewed upon its submission.

Orig NDA
HFD-570/Division file
HFD-570/Sun
HFD-570/Trout

1 Page(s) Withheld

Consult #930

REQUEST FOR TRADEMARK REVIEW

To: Labeling and Nomenclature Committee
Attention: Dan Boring, Chair (HFD-530), 9201 Corporate Blvd, Room N461

From:	**Division of** Pulmonary Drug Products	**HFD-570**
	Attention: Gretchen Trout	**Phone:** 827-1058

Date: December 11, 1997

Subject: Request for Assessment of a Trademark for a Proposed New Drug Product

Proposed Trademark: Pulmicort Respules	**NDA/ANDA#** 20-929

Established name, including dosage form:
Pulmicort Respules (budesonide nebulizing suspension)

Other trademarks by the same firm for companion products:
Pulmicort Turbuhaler (budesonide inhalation powder)

Indications for Use (may be a summary if proposed statement is lengthy):

[redacted]

Initial Comments from the submitter (concerns, observations, etc.):

Note: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

Rev. December 95

CONSULT #930

LNC TRADEMARK REVIEW

TO: HFD-570

ATTN: Gretchen Trout

PROPOSED NAME(S): Pulmicort Respules

ESTABLISHED NAME: The Committee believes the established name for this product should be -

budesonide inhalation suspension

COMMITTEE'S COMMENTS:

Since Pulmicort is a marketed trademark, the Committee considered the appropriateness of the name Respules and finds this name acceptable.

The Committee has no reason to find the proposed name unacceptable.

/S/ 3/1/96

Dan Boring, Ph.D., Chairman
Labeling and Nomenclature Committee