

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-127

ADMINISTRATIVE DOCUMENTS



Azelastine Eye Drops
Patent Certification

Patent Number: 5,164,194

Expiry Date: 11/01/2010

Type of Patent: Medicament for nasal use or for the eye containing as active ingredient azelastine or a physiologically acceptable salt

Name of Patent Owner: ASTA Pharma Aktiengesellschaft, Fed. Rep. of Germany ¹⁾

Name and Address of Agent: Dr. Juergen Bachmann, AWD, Fed. Rep. of Germany ²⁾

Original Declaration:

The undersigned declares that Patent No. 5,164,194 covers the formulation, composition and/or method of use of Azelastine Eye Drops. This product is the subject of this application for which approval is being sought.

Dr. Juergen Bachmann
Patent Specialist
AWD
Dresden, Fed. Rep. of Germany

- 1) ASTA Medica Aktiengesellschaft had been named at the time of patent approval ASTA Pharma Aktiengesellschaft
- 2) AWD is a 100% owned subsidiary of ASTA Medica Aktiengesellschaft

EXCLUSIVITY SUMMARY for NDA # 21-127
Trade Name OPTIVAR Generic Name Azelastine Hydrochloride
Ophthalmic Solution, 0.05
Applicant Name Asta Medica HFD- 550
Approval Date May, 2000

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 questions about the submission.

a) Is it an original NDA? YES / XX / NO / ___ /

b) Is it an effectiveness supplement? YES / ___ / NO / ___ /

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 / XX / 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 / XX / NO / ___ /

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

e) Has pediatric exclusivity been granted for this Active Moiety?

YES / X / NO / ___ /

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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 / XX /

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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

YES / ___ / NO / XX /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (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 / XX / NO / /

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

NDA # 20-114 _____

NDA # _____

NDA # _____

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 / XX /

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 9. 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 / XX / NO / ___ /

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (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 / XX / 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 9:**

- (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 / XX / NO / ___/

- (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 / XX /

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 / ___ /

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:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" 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 / XX /

Investigation #2 YES / ___ / NO / XX /

Investigation #3 YES / ___ / NO / ___ /

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

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

- (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 / XX /

Investigation #2 YES /___/ NO / XX /

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

Study # 400-301 Study # 2982

Study # 2983 Study # 2985

Study # _____ Study # 3021

- (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"):

Investigation # , Study # ALL Studies

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 # YES / XX / NO / / Explain:
All Studies

Investigation #2

IND # YES / / 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

(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 /XX/

If yes, explain: _____

/S/
Signature of Preparer
Title: Project Manager

5/18/2000
Date

/S/
Wiley A. Chambers, M.D.
Deputy Director
HFD-550

5/20/00
Date

cc:
NDA 21-127
HFD-550/DivFile
HFD-550/PM/Rodriguez
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi



AZELASTINE OPHTHALMIC SOLUTION

Title: Claimed Exclusivity

In accordance with 314.108(b)(4) ASTA Medica, Inc. is claiming an exclusivity period of three years for AZELASTINE OPHTHALMIC SOLUTION. Azelastine Hydrochloride in a nasal spray was approved for the treatment of seasonal allergic rhinitis under NDA# 20,114 from Wallace Laboratories on November 1, 1996.

This NDA is for an ophthalmic formulation, to be used for the prevention and relief of the signs and symptoms of allergic conjunctivitis.

The drug product, AZELASTINE OPHTHALMIC SOLUTION, containing the same active ingredient with the same conditions of approval, has not been previously approved.

A clinical development program for Azelastine Hydrochloride Eye Drops was conducted by our parent company ASTA Medica AG in Europe. Five of these studies; four in adults (2967, 2982, 2983, 2985) and one in pediatric patients (3021) are adequate and well controlled studies essential to approval of Azelastine Hydrochloride Eye Drops for the prevention and relief of the signs and symptoms of allergic conjunctivitis in adults and children.

In December 1997, ASTA Medica, Inc. filed an IND for AZELASTINE OPHTHALMIC SOLUTION IND [REDACTED]. The clinical study conducted under this IND, Study #400-301, is an adequate and well-controlled study demonstrating the efficacy of Azelastine Hydrochloride 0.05 Ophthalmic Solution. This study was designed in accordance with the recommendations from the Division of Anti-inflammatory, Analgesic & Ophthalmic Drug Products at FDA.

The other clinical studies included in this NDA were sponsored, conducted and funded by our parent company ASTA Medica AG. A list of the clinical investigations other than bioavailability or bioequivalence studies, conducted by Muro/ASTA Medica, Inc. and its parent company, ASTA Medica AG, together with the location of the study in the Clinical Data Section of the NDA is attached. Please note that ASTA Medica, Inc. and Muro Pharmaceutical, Inc. are both wholly owned subsidiaries of ASTA Medica AG.

To the best of our knowledge, published studies are not sufficient to form the basis of a finding of substantial evidence of effectiveness for Azelastine Hydrochloride Ophthalmic Solution 0.05%.

We believe that the above referenced studies are essential to the approval of this NDA for Azelastine Hydrochloride Ophthalmic Solution 0.05%. There are no publications of studies which were not sponsored by ASTA Medica that meet FDA's definition of adequate and well-controlled studies which could be used to document the efficacy and safety of Azelastine Hydrochloride Ophthalmic Solution 0.05%.

Based on these data, we conclude that the studies included in this submission were essential for the approval of AZELASTINE HYDROCHLORIDE OPHTHALMIC SOLUTION 0.05%. As a result, we are requesting 3 years of exclusivity upon approval of this NDA.



AZELASTINE OPHTHALMIC SOLUTION

On April 8, 1999, we filed a request for a written request for pediatric studies. We received the corresponding written request from FDA on April 16, 1999. This letter was superceded by the May 3, 1999 letter which is attached. The studies included in this NDA include the required pediatric studies. (Studies 3062, 3034 and 3021)

We are requesting a waiver of the requirement to conduct studies in pediatric patients below the age of 4 because allergic conjunctivitis is not a significant disease in this age group and as a result is not likely to be used by a substantial number of pediatric patients below the age of 4.

We are requesting an additional 6 months of exclusivity based on the submission of pediatric studies in this NDA.

A handwritten signature in black ink, appearing to read "Aileen Ryan".

Aileen Ryan
Director of Regulatory Affairs
ASTA Medica, Inc.

Add New Pediatric Information to this Submission

User Information

Preparer	RAPHAEL RODRIGUEZ
Title	PROJECT MANAGER/CONSUMER SAFETY OFFICER
Division	HFD-550

Application Information

Application Number	021127
Application Clock Date	1999-08-04 00:00:00
Application Type	N
Applicant Sponsor	ASTA MEDICA (US)
Drug Trade Name	AZELASTINE HCL OPHTHALMIC SOLUTION 0.05%
Drug Generic Name	AZELASTINE HCL OPHTHALMIC SOLUTION 0.05%
(leave Supplement Type, Number and Date blank, ONL you are entering an original application)	
Supplement Type	
Supplement Number TYPE NUMBER ONLY	
Supplement Date	
Proposed Indication(s)	For the treatment of itching of the eye associated with allergic conjunctivitis.
Has Proposed Indication been Approved?	<input type="checkbox"/> Check for YES
Adequacy of proposed label for Pediatric Dosing	Adequate for SOME pediatric age groups
Regulatory Action	Approved
Is there a Pediatric Phase 4 Commitment in the Action Letter for the Original Submission?	<input type="checkbox"/> Check if YES
Comments & Recommendations (please date)	5/16/200 The studies support all ages above 3 years.
Is there Pediatric Studies in this Submission? Select One	<input checked="" type="radio"/> YES, Pediatric data exists for at least one proposed indi which supports pediatric approval <input type="radio"/> YES, Pediatric data exists for at least one proposed indi but is inadequate to support pediatric approval <input type="radio"/> NO, no data was submitted for this indication, however, ongoing studies exist for pediatric patients <input type="radio"/> NO, Pediatric Studies are not necessary because of pedi <input type="radio"/> NO, No waiver and no pediatric data

User Information

Preparer	RAPHAEL RODRIGUEZ
Title	PROJECT MANAGER/CONSUMER SAFETY OFFICER
Division	HFD-550
Appl_No	21127
Suppl_No	0
Drug Name	AZELASTINE HCL OPHTHALMIC SOLUTION 0.05%

Additional Application Information - Enter any fields that apply

Dosage Form (COMIS)	DRP
Dosage Form (User-Selected)	Solution/Drops; Ophthalmic
Select Intended Pediatric Ages	
NeoNates: 0-30 days	<input type="checkbox"/>
Infants 1-24 months	<input type="checkbox"/>
Children 25 months - 12 years	<input type="checkbox"/>
Adolescents 13 - 16 years	<input type="checkbox"/>
Other Age Range:	<input checked="" type="checkbox"/> Please Define Age Range all ages above 3
Formulation Status:	
Are Further Studies Needed?	No further STUDIES are needed
If Studies ARE NEEDED:	
Comments & Recommendations (please date)	5/16/200 The studies suppo above 3.
Save and Continue	

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number: 21127 **Trade Name:** AZELASTINE HCL OPHTHALMIC SOLUTION 0.05%
Supplement Number: **Generic Name:** AZELASTINE HCL OPHTHALMIC SOLUTION 0.05%
Supplement Type: **Dosage Form:** Solution/Drops; Ophthalmic
Regulatory Action: AP **Proposed Indication:** For the treatment of itching of the eye associated with allergic conjunctivitis.

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

YES, Pediatric data exists for at least one proposed indication which supports pediatric approval

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)
 Other Age Groups (listed): all ages above 3

Label Adequacy Adequate for SOME pediatric age groups
Formulation Status
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:
5/16/200 The studies support all ages above 3.

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

Signature: [Signature] Date: 5/16/2000

PEDIATRIC EXCLUSIVITY DETERMINATION CHECKLIST

PART I - TO BE COMPLETED BY THE REVIEWING DIVISION. UPON COMPLETION FORWARD TO THE PEDIATRIC EXCLUSIVITY BOARD, HFD-002.

Date of Written Request from FDA 5/3/99 Application Written Request was made to: ND (IND#) _____
Timeframe Noted in Written Request for Submission of Studies 11 at time of NDA submission
NDA# 21-127 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6 SE7 SE8 SLR
Sponsor Asta Medica
Generic Name azelastine HCl oph'ic sol'n Trade Name _____
Strength 0.05% Dosage Form/Route ophthalmic solution
Date of Submission of Reports of Studies 8/3/99 Received 8/4/99
Pediatric Exclusivity Determination Due Date (60 or 90 days from date of submission of studies) 11/2/99

Table with 3 columns: Question, Yes/No, and a shaded area. Rows include: 'Was a formal Written Request made for the pediatric studies submitted?', 'Were the studies submitted after the Written Request?', 'Were the reports submitted as a supplement, amendment to an NDA, or NDA?', 'Was the timeframe noted in the Written Request for submission of studies met?', 'If there was a written agreement, were the studies conducted according to the written agreement? OR If there was no written agreement, were the studies conducted in accord with good scientific principles?', 'Were the studies responsive to the terms of the Written Request?'.

FORWARD TO THE PEDIATRIC EXCLUSIVITY BOARD, HFD-002.

PART II - TO BE COMPLETED BY THE PEDIATRIC EXCLUSIVITY BOARD

Pediatric Exclusivity [X] Granted ___ Denied
Existing Patent or Exclusivity Protection:
NDA/Product # Eligible Patents/Exclusivity Current Expiration Date

Pediatric exclusivity will apply to all patents and exclusivities listed for NDA 21-127 upon approval.

SIGNED [Signature] DATE
cc:
Archival NDA/IND ##-###

Originator: Deputy Center Director (Review Management)
October 6, 1998

cc:

IND:

NDA 21-127

HFD-550/Division file

HFD-550/MO/Chambers

HFD-550/PM/Rodriguez

HFD-550/Clin Rev/Holmes

HFD-93/Division of Data Management Services

HFD-600/Office of Generic Drugs

HFD-2/MLumpkin

HFD-104/DMurphy

HFD-6/KRoberts

PEDIATRIC EXCLUSIVITY DETERMINATION CHECKLIST



NEW DRUG APPLICATION
FD FORM 356H

AZELASTINE OPHTHALMIC SOLUTION

Title: Debarment Certification

This is to certify that ASTA Medica did not and will not use in any capacity the services of any person debarred under subsections (a) or (b) {section 306(a) or (b)}, in connection with this NDA application for Azelastine Ophthalmic Solution.

A handwritten signature in cursive script, appearing to read "Aileen Ryan".

Aileen Ryan
Director of Regulatory Affairs
ASTA Medica, Inc.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: GMB No. XXXX-XXXX
Expiration Date: XX/XX/XX

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- 1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	Mitchell Friedlaender MD	

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Rainer Skrotzki	TITLE CFO
FIRM/ORGANIZATION ASTA Medica, Inc.	
SIGNATURE <i>Rainer Skrotzki</i>	DATE 4/26/99

Paperwork Reduction Act Statement

All agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, to the address on the right.

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

Please DO NOT RETURN this form to this address.

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	See attached list	

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Rainer Skrotzki	TITLE CFO
FIRM/ORGANIZATION ASTA Medica, Inc.	
SIGNATURE <i>Rainer Skrotzki</i>	DATE 5/3/99

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right.

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

Please DO NOT RETURN this form to this address.