CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-201s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 7/31/10
See OMB Statement on Page 3.

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

NDA NUMBER
21-201

NAME OF APPLICANT/NDA HOLDER
Chemische Fabrik Kreussler & Co. GmbH

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
Asclera

ACTIVE INGREDIENT(S)	STRENGTH(S)
Polidocanol	0.5% and 1%

DOSAGE FORM
Injectable

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
d. Name of Patent Owner	Address *(of Patent Owner)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☐ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
2.3 If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3.**		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☐ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☐ No
2.7 If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☐ No
3.3 If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
4.2 Patent Claim Number(s) *(as listed in the patent)*	Does (Do) the patent claim(s) referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☐ No	
4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the proposed labeling.)*	

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☒ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
Howard Smith	6 January 2010

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Howard M. Smith	
Address INC Research 650 Peter Jefferson Parkway, Suite 200	City/State Charlottesville, VA
ZIP Code 22911	Telephone Number (Office) 434-244-5110; (Mobile) (b) (6)
FAX Number *(if available)* 919-882-0493	E-Mail Address *(if available)* hsmith@incresearch.com

inc
Research

September 29, 2003

Food and Drug Administration
Division of Dermatologic and Dental Drug Products
HFD-540
9201 Corporate Boulevard
Rockville, MD 20850

RE: PATENT INFORMATION

Neither the drug substance, polidocanol, nor the drug product, Aethoxysklerol, is currently under patent in either the United States or Europe.

Howard M. Smith

Sr. Director, Regulatory Operations
and Medical Writing

EXCLUSIVITY SUMMARY

NDA # 21201 SUPPL # HFD #

Trade Name Asclera

Generic Name polidocanol

Applicant Name Chemische Fabrik Kreussler & Co., GmbH

Approval Date, If Known March 30, 2010

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy 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 a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

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 ☒ 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 ☐

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

5

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

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

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

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 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 ☐ NO ☒

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

NDA#

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 ☒

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. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs 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 ☐ 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 ☐ 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:

(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 ☐

(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 ☐

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:

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 "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 ☐

Investigation #2 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:

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 ☐

Investigation #2 YES ☐ NO ☐

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"):

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 ☐ ! NO ☐
! Explain:

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 ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! 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 ☐

If yes, explain:

==========

Name of person completing form: Michael Monteleone
Title: Regulatory Project Manager
Date: 01/05/10

Name of Office/Division Director signing form: Norman Stockbridge
Title: Director, Division of Cardiovascular and Renal Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21201	ORIG-1	CHEMISCHE FABRIK KREUSSLER & CO. GMBH	Asclera (polidocanol) 0.5%/1%

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MICHAEL V MONTELEONE
03/30/2010

NORMAN L STOCKBRIDGE
03/30/2010

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 21-201 Supplement Number: _____ NDA Supplement Type (e.g. SE5): SE 1

Division Name:Cardiovascular and Renal Products PDUFA Goal Date: 01/10/10 Stamp Date: 7/10/2009

Proprietary Name: Asclera

Established/Generic Name: polidocanol

Dosage Form: Injection

Applicant/Sponsor: Chemische Fabrik Kreussler & Co., GmbH

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):
(1) _____
(2) _____
(3) _____
(4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s):1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: Sclerotherapy of C1 veins:

Group S: (<1 mm diameter; spider veins, (b) (4) , very small varicose veins)

Group R: (b) 1–3 mm diameter; reticular varices and small varicose veins)

Q1: Is this application in response to a PREA PMR? Yes ☐ Continue

No ☒ Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #:_____ PMR #:_____

Does the division agree that this is a complete response to the PMR?

☐ Yes. Please proceed to Section D.

☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW ☐ active ingredient(s) (includes new combination); ☒ indication(s); ☐ dosage form; ☐ dosing regimen; or ☐ route of administration?*

(b) ☐ No. PREA does not apply. **Skip to signature block.**

**** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.***

Q3: Does this indication have orphan designation?

☐ Yes. PREA does not apply. **Skip to signature block.**

☒ No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

☒ Yes: (Complete Section A.)

☐ No: Please check all that apply:

- ☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)
- ☐ Deferred for some or all pediatric subpopulations (Complete Sections C)
- ☐ Completed for some or all pediatric subpopulations (Complete Sections D)
- ☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
- ☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

☒ Necessary studies would be impossible or highly impracticable because:

- ☒ Disease/condition does not exist in children
- ☐ Too few children with disease/condition to study
- ☐ Other (e.g., patients geographically dispersed): _____

☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.

☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☒ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failedΔ
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

\# Not feasible:

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- ☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4)

additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as

pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Q1: Does this indication have orphan designation?

- ☐ Yes. PREA does not apply. **Skip to signature block.**
- ☐ No. Please proceed to the next question.

Q2: Is there a full waiver for all pediatric age groups for this indication (check one)?

- ☐ Yes: (Complete Section A.)
- ☐ No: Please check all that apply:
  - ☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - ☐ Deferred for some or all pediatric subpopulations (Complete Sections C)
  - ☐ Completed for some or all pediatric subpopulations (Complete Sections D)
  - ☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - ☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

  (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failedΔ
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

\# Not feasible:

☐ Necessary studies would be impossible or highly impracticable because:

- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease/condition to study
- ☐ Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the

drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for some or all pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 6/2008)

Section A:

Justification for full pediatric waiver

Varicose veins of the lower extremities is a disease that is not present in the pediatric population.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21201	ORIG-1	CHEMISCHE FABRIK KREUSSLER AND CO GMBH	AETHOXYSKLEROL (POLIDOCANOL)0.5%/1% (b) (4)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MICHAEL V MONTELEONE
11/17/2009

Pediatric Research and Equity Act Waivers

IND/NDA/BLA #: 21-201 Supplement Type: Supplement Number:

Product name and active ingredient/dosage form: Asclera (polidocanol) 0.5% & 1.0% injection

Sponsor: Chemische Fabrik Kreussler & Co., GmbH

Indications(s):

Sclerotherapy of C1 veins:
Group S: (<1 mm diameter; spider veins, (b) (4) very small varicose veins)
Group R: (b) 1-3 mm diameter; reticular varices and small varicose veins)

(NOTE: If the drug is approved for or Sponsor is seeking approval for more than one indication, address the following for each indication.)

1. Pediatric age group(s) to be waived.
    a. Full waiver

2. Reason(s) for waiving pediatric assessment requirements (choose all that apply **and provide justification**):

    a. Studies are impossible or highly impractical (e.g. the number of pediatric patients is so small or is geographically dispersed). If applicable, chose from adult-related conditions in Attachment I
        i. Varicose veins of the lower extremities is a disease that is not present in pediatric populations.

Attachment I

Adult-Related Conditions that do not occur in pediatrics and qualify for a waiver
These conditions qualify for waiver because studies would be impossible or highly impractical

Age-related macular degeneration
Alzheimer's disease
Amyotrophic lateral sclerosis
Atherosclerotic cardiovascular disease
Benign prostatic hypertrophy
Chronic Obstructive Pulmonary Disease
Erectile Dysfunction
Infertility
Menopausal and perimenopausal disorders
Organic amnesic syndrome
(not caused by alcohol or other psychoactive substances)
Osteoarthritis
Parkinson's disease
Postmenopausal Osteoporosis
Vascular dementia/ Vascular cognitive disorder/impairment

Cancer:
- Basal cell
- Bladder
- Breast
- Cervical
- Colorectal
- Endometrial
- Gastric
- Hairy cell leukemia
- Lung (small & non-small cell)
- Multiple myeloma
- Oropharynx (squamous cell)
- Ovarian (non-germ cell)
- Pancreatic
- Prostate
- Renal cell
- Uterine

REQUEST FOR WAIVER OF PEDIATRIC STUDIES

IND/NDA/BLA Number (as applicable) 21-201

Sponsor: Chemische Fabrik Kreussler & Co., GmbH

Indication(s): Varicose veins of lower extremities

1. What age ranges are included in your waiver request? Birth to age 16

2. Reasons for waiving pediatric studies:

☐ a) No meaningful therapeutic benefit over existing treatments and is unlikely to be used in a substantial number of pediatric patients.

X b) Studies are impossible or highly impractical because the number of patients is so small or geographically dispersed.

☐ c) The product would be ineffective or unsafe in all pediatric age groups.

☐ d) Attempts to develop a pediatric formulation for a specific age group has failed.

☐ e) Disease-specific waiver indicated for the treatment of the condition in a (please check)

- ☐ Alzheimer's disease_Age-related macular degeneration
- ☐ Prostate Cancer_Breast cancer
- ☐ Renal cell cancer_Non-germ cell ovarian cancer
- ☐ Hair cell cancer_Pancreatic cancer, colorectal cancer
- ☐ Osteoarthritis_Squamous cell cancers of the oropharynx
- ☐ Uterine cancer_Basal cell and squamous cell cancer
- ☐ Endometrial cancer_Small cell and non-small cell lung cancer
- ☐ Parkinson's disease_Amyotrophic lateral sclerosis
- ☐ Arteriosclerosis_Symptoms of menopause
- ☐ Infertility Other (please state and justify)

3. Justification for waiver (not necessary if category 2e) is checked):

Varicose veins of the lower extremities is a disease that is not present in pediatric patients.

Chemische Fabrik Kreussler & Co. GmbH hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Date: 08 December 2009

Dr. Stephan C. Travers
Managing Director of Kreussler

Date: 14 December 2009

Howard M. Smith
US Agent for Kreussler

Chemische Fabrik Kreussler & Co. GmbH · Postanschrift: Postfach 12 04 54 · D-65082 Wiesbaden
Hausanschrift: Rheingaustrasse 87-93 · D-65203 Wiesbaden · Amtsgericht Wiesbaden HRB-Nr.: 2749
Telefon 0611 9271-0 · Telefax 0611 9271-111 · Internet: www.kreussler.com · E-Mail: info@kreussler.com
Geschäftsführer: Dr. Detlev Travers, Dr. Stephan Travers, Dr. Helmut Eigen

kreussler

16. July 2008

Debarment Certification Statement

Chemische Fabrik Kreussler & Co. GmbH hereby certifies that in connection with this application it did not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act.

Dr. Travers
Managing Director

Chemische Fabrik Kreussler & Co. GmbH
Rheingaustrasse 87-93
65203 Wiesbaden
Germany

Chemische Fabrik Kreussler & Co. GmbH Postanschrift: Postfach 12 01 51 D-65082 Wiesbaden
Hausanschrift: Rheingaustrasse 87-93 D-65203 Wiesbaden Amtsgericht Wiesbaden HRB-Nr. 2740
Telefon 06 11/ 92 71-0 Telefax 06 11/ 92 71-111 Internet: www.kreussler.de
Geschäftsführer: Dr. iur. Detlef Travers, Dr. iur. Stephan Travers, Dipl.-Ing. Rüdiger D. Hasenclever

inc Research

September 29, 2003

Food and Drug Administration
Division of Dermatologic and Dental Drug Products
HFD-540
9201 Corporate Boulevard
Rockville, MD 20850

RE: DEBARMENT CERTIFICATION

I certify that none of the investigators in the pivotal studies (OHIO and MICA) in this application are currently on, or have ever been on, the FDA's debarment list.

Howard M. Smith

Sr. Director, Regulatory Operations
and Medical Writing

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: April 30, 2009

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	

☐ (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	TITLE
Stephan Travers	Managing Director
FIRM/ORGANIZATION	
Chemische Fabrik Kruessler & Co GmbH	
SIGNATURE	**DATE**
H M Smythe U.S. Agent for Kruessler	21 July 2008

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

PSC Graphics: (301) 443-1090 EF

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]		
NDA # 021201 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: N/A Established/Proper Name: Polidocanol Dosage Form: Injection		Applicant: Chemische Fabrik Kreussler & Co., GmbH Agent for Applicant (if applicable): Inc Research
RPM: Michael Monteleone		Division: Cardiovascular and Renal Products

NDAs:	505(b)(2) Original NDAs and 505(b)(2) NDA supplements:
NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)	Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)): Provide a brief explanation of how this product is different from the listed drug. ☐ If no listed drug, check here and explain: **Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.** ☐ No changes ☐ Updated Date of check: **If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.** **On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.**

❖ User Fee Goal Date Action Goal Date (if different)	April 10, 2010 April 09, 2010 Action taken – March 30, 2010
❖ Actions	
• Proposed action	☒ AP ☐ TA ☐ AE ☐ NA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None 08-02-04 – Not Approvable 08-18-08 – Incomplete Response
❖ Promotional Materials *(accelerated approvals only)* Note: If accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see guidance http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received

[1] The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Application Characteristics [2]	

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only): NME

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC

Comments: _____

❖ Date reviewed by PeRC *(required for approvals only)* If PeRC review not necessary, explain: _____	12-09-09
❖ BLAs only: *RMS-BLA Product Information Sheet for TBP* has been completed and forwarded to OBPS/DRM *(approvals only)*	☐ Yes, date
❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Press Office notified of action (by OEP)	☒ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☐ None ☒ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[2] All questions in all sections pertain to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☐ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[3]	Yes
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) Approval 30 March 2010
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	Yes
• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Medication Guide/Patient Package Insert/Instructions for Use *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☒ None
• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	

[3] Fill in blanks with dates of reviews, letters, etc.

• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent division proposal for (only if generated after latest applicant submission)	Yes
• Most recent applicant-proposed labeling	Yes
❖ Proprietary Name • Review(s) *(indicate date(s))* • Acceptability/non-acceptability letter(s) *(indicate date(s))*	29 December 2009 Acceptable – 29 December 2009
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☐ RPM ☒ DMEDP 01/07/09 ☒ DRISK 12/30/09 ☒ DDMAC 12/08/09 ☐ CSS ☒ Other reviews SEALD 12/15/09 DMEPA 01/07/10
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)*	RPM Filing Review – 12-16-03 Filing Meeting Memo – 12-16-03 RPM Overview – 04-01-10
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☐ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant in on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☐ No ☐ Not an AP action
❖ Pediatric Page *(approvals only, must be reviewed by PERC before finalized)*	☒ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Outgoing communications *(letters (except previous action letters), emails, faxes, telecons)*	
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• PeRC *(indicate date of mtg; approvals only)*	☐ Not applicable 12-9-09
• Pre-Approval Safety Conference *(indicate date of mtg; approvals only)*	☐ Not applicable
• Regulatory Briefing *(indicate date of mtg)*	☐ No mtg

[4] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg
• Other (e.g., EOP2a, CMC pilot programs)	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☐ None 03/30/2010
Division Director Summary Review *(indicate date for each review)*	☐ None 12/22/2009
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 12/18/2009
PMR/PMC Development Templates *(indicate total number)*	☐ None
Clinical Information[5]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	
• Clinical review(s) *(indicate date for each review)*	11-16-09
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☐ None
❖ Safety update review(s) *(indicate location/date if incorporated into another review)*	Clinical Review (11/16/09) pg 35
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	Clincal Review (11/16/09) pg 10
❖ Clinical reviews from other clinical areas/divisions/Centers *(indicate date of each review)*	☐ None DDDP 07-13-04
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not needed
❖ Risk Management • REMS Document and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo *(indicate date)* • Review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☐ None 12/30/2009
❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested 11/18/09
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ None 11/25/09

[5] Filing reviews should be filed with the discipline reviews.

Statistical Review(s) *(indicate date for each review)*	☐ None 11/17/09
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☐ None 11/25/09
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 11/25/09
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	☐ None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ None 12/24/09
• Supervisory Review(s) *(indicate date for each review)*	☐ None 11/18/09
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 11/18/09
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☐ None 03/18/2010
• Product quality review(s) *(indicate date for each review)*	☐ None 03/18/2010
• ONDQA Biopharmaceutics review *(indicate date for each review)*	
• BLAs only: Facility information review(s) *(indicate dates)*	☐ None
❖ Microbiology Reviews • NDAs: Microbiology reviews (sterility & pyrogenicity) *(indicate date of each review)* • BLAs: Sterility assurance, product quality microbiology *(indicate date of each review)*	12/21/09 ☐ Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	12/03/09
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	

• NDAs: Facilities inspections (include EER printout) *(date completed must be within 2 years of action date)*	Date completed: 03/17/2010 ☒ Acceptable ☐ Withhold recommendation
• BLAs: o TBP-EER o Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) *(date completed must be within 60 days prior to AP)*	Date completed: ☐ Acceptable ☐ Withhold recommendation Date completed: ☐ Requested ☐ Accepted ☐ Hold
❖ NDAs: Methods Validation	☒ Completed ☐ Requested ☐ Not yet requested ☐ Not needed

Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21201	ORIG-1	CHEMISCHE FABRIK KREUSSLER & CO. GMBH	Asclera (polidocanol) 0.5%/1%

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/s/

MICHAEL V MONTELEONE
04/01/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PDUFA GOAL DATE EXTENSION

NDA 021201

Chemische Fabrik Kreussler & Co., GmbH.
Attention: Stephan Travers, M.D.
Rheingaustrasse 87-93
D-65203 Wiesbaden
Germany

Dear Dr. Travers:

Please refer to your new drug application (NDA) originally submitted October 1, 1999, withdrawn December 1, 1999 and resubmitted September 29, 2003 and July 10, 2009, under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Asclera (polidocanol) 0.5% and 1% Injection.

On December 16 2009, we received your December 15, 2009, major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is April 10, 2010.

If you have any questions, please call Michael Monteleone, Regulatory Project Manager, at (301) 796-1952.

Sincerely yours,

{See appended electronic signature page}

Edward Fromm, RPh., RAC
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Cc:
Howard Smith, INC Research
675 Peter Jefferson Parkway
Suite 120
Charlottesville, VA 22911

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21201	ORIG-1	CHEMISCHE FABRIK KREUSSLER & CO. GMBH	Asclera (polidocanol) 0.5%/1%

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/s/

EDWARD J FROMM
01/08/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21-201

INFORMATION REQUEST

INC Research
Attention: Howard M. Smith
Assistant Director, Med. Writing
650 Peter Jefferson Parkway, Suite 200
Charlottesville, VA 22911

Dear Mr. Smith:

Please refer to your March 31, 2009 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Polidocanol Injection.

We reviewed your submission dated December 23, 2009 and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

We note your explanation for not including the requested IR identification test in the release specification on page 3. (see explanation below)

> The HPLC-test for Assay of polidocanol (page 3) to which you refer in your e-mail is performed on the semi-finished product (filled naked ampoules) BEFORE labeling and packaging. It was never requested and would not make sense to change this test.
>
> Then, AFTER labeling and packaging, the Identity test will be performed -as requested during the phone conference- with the IR-test on the finished product.

However, if these tests are conducted on the filled naked ampoules before labeling and packaging, we do not consider these tests release tests for the final drug product. This testing should be conducted on the finished drug product to ensure the identity, purity, and quality of the drug product. As we believe that the labeling and packaging operations will not alter the drug product, the results from these tests could be used as part of the final drug product release. In an effort to resolve this issue, we recommend the following action:

The final drug product release specification tables should include all tests, along with their acceptance criteria, conducted on the drug product before (filled naked ampoules) and after (final drug product) labeling and packaging. Identify those tests conducted on the filled naked ampoules with an asterisk and include a footnote indicating that these tests are conducted on the filled naked ampoules prior to labeling and packaging. Submit the final drug product release specification for each drug product strength which should include all tests originally submitted in the tables on pages 3 and 4 of your December 28, 2009 submission as well as the tests included in the table in your January 5, 2010 email.

If you have any questions, call Don Henry, Regulatory Project Manager, at (301) 796-4227.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21201	ORIG-1	CHEMISCHE FABRIK KREUSSLER & CO. GMBH	Asclera (polidocanol) 0.5%/1%

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/s/

RAMESH K SOOD
01/06/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21-201

INFORMATION REQUEST

INC Research
Attention: Howard M. Smith
Assistant Director, Med. Writing
650 Peter Jefferson Parkway, Suite 200
Charlottesville, VA 22911

Dear Mr. Smith:

Please refer to your March 31, 2009 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Polidocanol Injection.

We are reviewing the container label and carton labeling of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Use of the company logo is acceptable provided the full company name is printed.
2. Strength per single milliliter should be expressed as mg per mL for both container labels and carton labeling. Change the references of strength (when expressed in terms of one milliliter) from XX mg per 1 mL to XX mg per mL.
3. Add a space between the numerals and units printed on the container labels and carton labeling. Spaces were removed from between all of the numerals and units on this revised version. This can be confusing and lead to misinterpretation

If you have any questions, call Don Henry, Regulatory Project Manager, at (301) 796-4227.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21201	ORIG-1	CHEMISCHE FABRIK KREUSSLER AND CO GMBH	Asclera (polidocanol) 0.5%/1%

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/s/

RAMESH K SOOD
12/30/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21-201

INFORMATION REQUEST

INC Research
Attention: Howard M. Smith
Assistant Director, Med. Writing
650 Peter Jefferson Parkway, Suite 200
Charlottesville, VA 22911

Dear Mr. Smith:

Please refer to your March 31, 2009 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Polidocanol Injection.

We are reviewing the container label and carton labeling of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

A. Container Label

1. The abbreviation "IV" should be spelled out as "Intravenous" on all of the labels and labeling to reduce the potential for misinterpretation of the abbreviation.
2. Replace the statement (b) (4) on the principal display panel with the statement "Single use: Discard unused portion".
3. Remove the swoosh line between the proprietary name and the established name on the container label. There should be no intervening matter that appears between the proprietary name and the established name to comply with 21 CFR 201.10(a).
4. Ensure the established name is at least ½ the size and prominence of the proprietary name to comply with 21 CFR 201.10(g)(2). The proprietary name, established name, and strength should be the most prominent information communicated on the principal display panel.
5. The presentation of strength on the container label, "0.5%", is difficult to read as currently printed in white font inside the gray circular-shaped graphic. Revise the white font color to another prominent color to provide adequate contrast, thereby increasing the prominence of the strength.
6. Increase the font size of the circular graphics conveying the strength (0.5 % and 1 %) to improve readability on the small vial.
7. Modify the word "ampoule" to read "ampule" for the correct American-English spelling.
8. Revise the unit "ml" to read as "mL". The lowercase letter 'l' can be confusing and look like the number '1'.
9. The vial label lacks information regarding the manufacturer of Asclera. The manufacturer information should be included on all labels and labeling.

10. Revise the strength statements "5 mg/1 ml" and "10 mg/1 ml" to read as "5 mg per mL" and "10 mg per mL" (or "5 mg/mL" and "10 mg/mL"). The use of a slash with the number "1" is easily misinterpreted. The United States Pharmacopeia 30/National Formulary 25 (USP 30/NF 25) states that "1 mL" not be used when expressing strength per single milliliter. Strength per single milliliter should be expressed as mg/mL or mg per mL.

B. Carton Labeling

1. In accordance with 21 CFR 201.100 (a)(5), include the quantitative information about the inactive ingredients
2. Relocate the statement "Each ampoule intended for immediate use in a single patient" on the back panel of the carton label to the front on the principal display panel and replace it with "Single use: Discard unused portion".
3. Remove the swoosh line between the proprietary name and the established name on the carton label. There should be no intervening matter that appears between the proprietary name and the established name to comply with 21 CFR 201.10(a).
4. Ensure the established name is at least ½ the size and prominence of the proprietary name to comply with 21 CFR 201.10(g)(2). The proprietary name, established name, and strength should be the most prominent information communicated on the principal display panel.
5. The presentation of strength on the container label, "0.5%", is difficult to read as currently printed in white font inside the gray circular-shaped graphic. Revise the white font color to another prominent color to provide adequate contrast, thereby increasing the prominence of the strength.
6. Add a net quantity statement such as, "contains 5 ampules each containing 10 mg/2 mL", to the principal display panel. It is important for healthcare professionals to determine the net contents of the carton in terms of the number of ampules contained inside.
7. Modify the word "ampoule" to read "ampule" for the correct American-English spelling.
8. Revise the unit "ml" for milliliter to read as "mL". The lowercase letter 'l' can be confusing and look like the number '1'.
9. In the NDA submission, the Applicant is stated as "Chemische Fabrik Kreussler & Co., GmbH", however the carton labeling states the Applicant as Kreussler & Co., GmbH, Germany". The manufacturer name should be identical and consistent on all labels and labeling. Revise accordingly.
10. Replace the font used for "kreussler" on the drug product carton labels with a block-type font to improve readability.
11. Revise the strength statements "5 mg/1 ml" and "10 mg/1 ml" to read as "5 mg per mL" and "10 mg per mL" (or "5 mg/mL" and "10 mg/mL"). The use of a slash with the number "1" is easily misinterpreted. The United States Pharmacopeia 30/National Formulary 25 (USP 30/NF 25) states that "1 mL" not be used when expressing strength per single milliliter. Strength per single milliliter should be expressed as mg/mL or mg per mL.

If you have any questions, call Don Henry, Regulatory Project Manager, at (301) 796-4227.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21201	ORIG-1	CHEMISCHE FABRIK KREUSSLER AND CO GMBH	AETHOXYSKLEROL (POLIDOCANOL)0.5%/1% (b) (4)

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/s/

RAMESH K SOOD
12/17/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21-201

INFORMATION REQUEST

INC Research
Attention: Howard M. Smith
Assistant Director, Med. Writing
650 Peter Jefferson Parkway, Suite 200
Charlottesville, VA 22911

Dear Mr. Smith:

Please refer to your March 31, 2009 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Polidocanol Injection.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

(b) (4)

If you have any questions, call Don Henry, Regulatory Project Manager, at (301) 796-4227.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21201	ORIG-1	CHEMISCHE FABRIK KREUSSLER AND CO GMBH	AETHOXYSKLEROL (POLIDOCANOL)0.5%/1% (b) (4)

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/s/

RAMESH K SOOD
11/30/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21-201

INFORMATION REQUEST

INC Research
Attention: Howard M. Smith
Assistant Director, Med. Writing
650 Peter Jefferson Parkway, Suite 200
Charlottesville, VA 22911

Dear Mr. Smith:

Please refer to your March 31, 2009 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Polidocanol Injection.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. We acknowledge your conversion to the polidocanol assay HPLC method as the regulatory method for identification of polidocanol in the finished drug product. However, the use of relative retention time alone as the test for identification is not considered specific as outlined in ICH Q6A. Revise the drug product specification for both strengths to include an additional polidocanol identification test. As you are currently using a HPLC method, we would consider the addition of a specification "UV absorbance spectrum matches that of the reference standard" as an acceptable approach. Provide the revised drug product specifications, including all other changes since your July 2009 resubmission, for review during this review cycle.

2. Revise the drug product carton and container labels based on the following four comments:

    a. Include the drug product dosage form "Injection" in the drug product name. Enclose "polidocanol" in parentheses in the drug product name.

    b. Include the expression of content per total volume prior to and more prominently than the expression of content per mL.

    c. Include the statement "Each ampoule intended for immediate use in a single patient" on the carton and container labels.

    d. As the USAN name for the drug substance is polidocanol, remove the reference to (b) (4) from all carton and container labels intended for the US market.

Based on our review of your responses to our information request dated 30-OCT-2009, we note the following:

1. We find your rationale for the lack of extractables testing to be acceptable. Therefore, we will not require extractables testing.

2. We find your rationale for the inclusion of bacterial endotoxins and sterility testing at the beginning and end of the stability program to be acceptable. Therefore, we will not require additional annual testing for these properties as part of the stability program.

If you have any questions, call Don Henry, Regulatory Project Manager, at (301) 796-4227.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21201	ORIG-1	CHEMISCHE FABRIK KREUSSLER AND CO GMBH	AETHOXYSKLEROL (POLIDOCANOL)0.5%/1% (b) (4)

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/s/

RAMESH K SOOD
11/19/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21-201

INFORMATION REQUEST

INC Research
Attention: Howard M. Smith
Assistant Director, Med. Writing
650 Peter Jefferson Parkway, Suite 200
Charlottesville, VA 22911

Dear Mr. Smith:

Please refer to your March 31, 2009 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Polidocanol Injection.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Your current analytical method used to identify the drug substance in the drug product is not considered specific. In accordance with ICH Q6A, either convert this analytical method to a method considered specific, such as infrared spectroscopy, or include an additional identification method for polidocanol in the drug product specification for both concentrations.
2. Report the actual values for (b) (4) and impurities in the drug substance instead of "complies."
3. Revise the drug product specification to include "free from visible particles" as part of the appearance requirement and delete the particulate matter – visible requirement.
4. Provide information on extractables testing conducted using the drug product as well as an assessment for needing further monitoring of extractables at drug product release and as part of the post-approval stability protocol.
5. Revise the post-approval stability protocol to include annual sterility and bacterial endotoxin testing of the drug product.
6. In accordance with 21 CFR 314.81 (b)(1)(ii), revise the post-approval stability commitment to include the reporting requirement for "*...information concerning any bacteriological contamination, or any significant chemical, physical, or other change or deterioration in the distributed drug product, or any failure of one or more distributed batches of the drug product to meet the specification established for it in the application.*"
7. Provide updated carton and container labels for the drug product.

If you have any questions, call Don Henry, Regulatory Project Manager, at (301) 796-4227.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21201	ORIG-1	CHEMISCHE FABRIK KREUSSLER AND CO GMBH	AETHOXYSKLEROL (POLIDOCANOL)0.5%/1% (b) (4)

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/s/

KASTURI SRINIVASACHAR
10/30/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21-201

ACKNOWLEDGE CLASS 2 RESPONSE

Chemische Fabrik Kreussler & Co., GmbH.
Attention: Stephan Travers, M.D.
Rheingaustrasse 87-93
D-65203 Wiesbaden
Germany

Cc:
Howard Smith, INC Research
675 Peter Jefferson Parkway
Suite 120
Charlottesville, VA 22911

Dear Dr. Travers:

We acknowledge receipt on July 10 of your July 10, 2009 resubmission to your new drug application for polidocanol, 0.5% and 1% Injectable

We consider this a complete, class 2 response to our August 18, 2008 action letter. Therefore, the user fee goal date is January 10, 2010.

If you have any questions, call Mike Monteleone, Regulatory Project Manager, at (301) 796-1952.

Sincerely,

{See appended electronic signature page}

Michael Monteleone
Regulatory Project Manager
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

MICHAEL V MONTELEONE
08/26/2009

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-201

Chemische Fabrik Kreussler & Co., GmbH.
Attention: Stephan Travers, M.D.
Rheingaustrasse 87-93
D-65203 Wiesbaden
Germany

Dear Dr. Travers:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (b) (4) (polidocanol) 0.5% and 1% Injectable.

We acknowledge receipt of your letter dated September 10, 2008 which provides a preliminary response to our incomplete response letter dated August 18, 2008.

We have reviewed your letter and have the following comments.

- With regard to the following two comments provided in our letter dated August 18, 2008:
    1. The sterilization validation information regarding the Aethoxysklerol® manufacturing process is not acceptable in the current state of transition from (b) (4) (old) facility to the newly constructed addition of what is now named (b) (4)

    2. In addition, the sterility information originally submitted in your NDA, perhaps adequate at the time of submission, is not current and therefore not acceptable for the sterility assurance of the product. All of the sterilization processes and the associated equipment should be re-qualified after installation at the new facility and the facility must be ready for inspection. The sterilization validation must include performance requalification data summary from the relocated sterilizers (i.e (b) (4) showing successful sterilization and depyrogenation of containers, closures, filling equipment and components which come in direct contact with the product.

In volume 3 page 124 "Note to reviewer" you state that it is important that the Agency is aware that (b) (4) has constructed an additional, modern facility adjacent to the original facility. Most of installation of the support system has been completed and the firm is purchasing new equipment as well as relocating the current equipment from the original facility to the new building. This means that all of the equipment (throughout the Aethoxysklerol® manufacturing process) that has been used to manufacture Aethoxysklerol® will be relocated to

the new facility. This equipment will be revalidated/requalified after being moved to the new building. This is (b) (4). Firm's current plant as stated on page 124, is to continue to manufacture Aethoxysklerol® ***on the same equipment in the new facility***. In this case, recent validation of the sterilization process, validation of the new equipment and re-qualification of the relocated old equipment will be necessary. The new facility must be ready for inspection at the time of your submission. It is our understanding that (b) (4) of the filled product is the only process step which will be carried out in Section 1 (old facility), in which case a recent (b) (4) re-qualification with appropriate load configuration for Aethoxysklerol® will suffice.

Therefore, the statement that (b) (4) facility is "old" is a non-issue. However, if you intend to manufacture at the old facility, then the question arises as to whether this facility is ready for inspection. Again, since you have clearly stated in your "note to the reviewer", that you intend to manufacture at the new facility, we look forward to your sterilization process validation package for your new facility. If there is any confusion in our understanding of your intent, please feel free to communicate that to us.

If you have any questions, please call Alisea Crowley, Regulatory Health Project Manager, at (301) 796-1144.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc: INC Research, Inc.
US Agent
Attention: Mr. Howard Smith
650 Peter Jefferson Parkway, Suite 200
Charlottesville, VA 22911

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/s/

Norman Stockbridge
10/14/2008 04:53:04 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Chemische Fabrik Kreussler & Co., GmbH.
Attention: Stephan Travers, M.D.
Rheingaustrasse 87-93
D-65203 Wiesbaden
Germany

Dear Dr. Travers:

We acknowledge receipt of your June 21, 2008 submission to your new drug application (NDA) for (b) (4) (polidocanol) 0.5% and 1% Injectable.

We do not consider this a complete response to our action letter. Therefore, the review clock will not start until we receive a complete response. The following deficiencies from our action letter still need to be addressed:

The sterilization validation information regarding the Aethoxysklerol® manufacturing process is not acceptable in the current state of transition from (b) (4) or from the (b) (4) (old) facility to the newly constructed addition of what is now named (b) (4). In addition, the sterility information originally submitted in your NDA, perhaps adequate at the time of submission, is not current and therefore not acceptable for the sterility assurance of the product. All of the sterilization processes and the associated equipment should be re-qualified after installation at the new facility and the facility must be ready for inspection. The sterilization validation must include performance requalification data summary from the relocated sterilizers (i.e. (b) (4) showing successful sterilization and depyrogenation of containers, closures, filling equipment and components which come in direct contact with the product.

If you have any questions, call Alisea Crowley, Pharm.D., Regulatory Project Manager, at (301) 796-1144.

Sincerely,

{See appended electronic signature page}

Edward Fromm, R.Ph.
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Russell Fortney
8/18/2008 04:56:30 PM
signing for Edward Fromm

:nc
Research®
4 Falls of Neuse Road
Su)0
Raleigh, NC 27609
tel: 919-876-9300
fax: 919-876-9360

Howard M. Smith certifies for Chemische Fabrik Kreussler & Co. GmbH that the field copy is a true copy of the application described in 21 CFR 314.50 (l)(3) and contained in the archival and review copies of the application.

Signature: Howard Smith

Date: 21 July 2008

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-201

Chemische Fabrik Kreussler & Co. GmbH
c/o INC Research
Attention: Mr. Howard M. Smith
675 Peter Jefferson Parkway
Suite 120
Charlottesville, VA 22911

Dear Mr. Smith:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Aethoxyskerol (polidicanol) Injectable 0.5%, 1%, (b) (4)

We acknowledge receipt of your December 9, 2005 email on dose-response (i.e. 2 concentration-controlled studies ASK 94-002, 96-001). However, we would like to review the actual data and detailed results of these two PK studies to make an evaluation of dose-response, and request that you submit the data and detailed results as soon as possible.

Pending receipt and review of the above, we suggest that blood sampling in the intended US-clinical study will be necessary to determine PK data and to address the issue of dose-response.

If you have any questions, please call:

Alisea Sermon, Pharm.D.
Regulatory Project Manager
(301) 796-1144

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Acting Division Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc: Stephan Travers, M.D.
Chemische Fabrik Kreussler & Co. GmbH
Postfach 12 04 54, D-65082 Wiesbaden
Rheingaustr. 87-93, D-65203 Wiesbaden

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/s/

Norman Stockbridge
12/20/2005 06:56:40 AM

Meeting Minutes

Meeting Date:	November 30, 2005
Type of Meeting:	Guidance
Classification:	Type C
IND Application:	NDA 21-201
Drug:	Aethoxyskerol
Sponsor:	Chemische Fabrik Kreussler & Co., GmbH c/o INC Research
Meeting Request Date:	November 2, 2005
Briefing Package Received:	November 22, 2005
Meeting Location:	Teleconference
Meeting Chair:	Norman Stockbridge, M.D., Ph.D.
Meeting Recorder:	Alisea Sermon, Pharm.D.

Attendees:

Division of Cardio-Renal Drug Products

Norman Stockbridge, M.D., Ph.D.	Acting Director
Khin Maung U, M.D.	Medical Officer
Alisea Sermon, Pharm.D.	Regulatory Health Project Manager

Kreussler

Stephan Travers, LLD	President
Joachim Otto	Medical Scientific Director

Background

The sponsor requested a teleconference to discuss Dr. Khin Maung U's electronic response, dated October 3, 2005, to Kreussler's "informal" email proposal dated, August 12, 2005 for Aethoxyskerol.

Meeting

After introductions, Dr. Stockbridge highlighted 3 issues to be discussed:

- **Long-term safety data**
- **Durability of treatment effect**
- **Dose Response**

Long-term Safety Data

Dr. Stockbridge noted that there is a registry in France that may have long-tem safety data; however he is unsure about the characteristics of the data and the adequacy of their follow-up procedures. The French registry may also have data and patients that can be used by Kreussler. He suggested that a subset of patients could be identified. For example, the sponsor could prospectively contact approximately 1000 patients to determine their long-term adverse events (from the time of the procedure to the time of the survey). He explained

that it would prevent the sponsor from having to enroll patients in a new study and collecting all new long-term safety data. For those reasons, he suggested that it is beneficial for Kreussler to try to gain access to the French registry. The sponsor agreed to Dr. Stockbridge's suggestion and also stated that it will try to contact the principle investigator directly.

Dr. Stockbridge stated that if Kreussler were unable to obtain the French registry, the Division would then require a larger exposure database than the 300 patients and will also require Kreussler to establish a US controlled post-marketing registry to supplement existing long term data. The sponsor replied that their current database has 300 to 340 patients. (b) (4) The sponsor agreed to make the commitment that only experienced and accredited phlebologists will be allowed to receive numbered boxes of drug product and that phebologists must provide a commitment to submit long-term safety data. Dr. Stockbridge reiterated that the Division will expect prospective data and is very reluctant to reduce any of the long-term safety data requirements. He encouraged Kreussler to contact the French phlebologists and, if successful, the Division may waive the US post-marketing registry requirement.

Durability of treatment effect

Dr. Stockbridge emphasized the importance of providing patients with a quantitative measure of treatment effect. He explained that there will be a minimum time frame for treatment duration that will be used to determine the approvability of the NDA. The sponsor said that they were prepared to accept restrictions in labeling if the Division was not satisfied with the duration of treatment. Dr. Stockbridge reiterated that the Division will not include a vague restriction description in labeling and encouraged Kreussler to study the time frame for varicose vein reappearance after treatment. The sponsor answered that it was not opposed to Dr. Stockbridge's recommendations and they are confident that once a vein is closed after 8 weeks, it will not reopen after 6 months. Kreussler agreed to provide the Division with the data to support the durability of treatment effect.

The sponsor voiced some concern about the pharmacokinetic requirements and explained that the collection of adequate PK data would probably take 2 days and patients would be less prone to enroll because of the inconvenience. Dr. Stockbridge responded that PK data would only have to be collected from a small number of patients and it may not be necessary for patients to stay in a clinic overnight in order to obtain a few time points. The sponsor also stated that it is unsure whether the plasma levels of the drug will be under the detection limit because a small concentration and a very small volume of study drug will be used in the proposed clinical study. Dr. Stockbridge replied that if it is not feasible to collect PK data, it will not be a cause to refuse approval of the NDA. However, the sponsor will be expected to make a reasonable effort to collect sufficient PK data. The sponsor asked if the Division could use the PK data submitted for Aethoxyskerol 3%. Dr. Stockbridge responded that he would have to have a clinical pharmacologist review the data before he could comment. The sponsor offered to submit a PDF file of the PK data and send it to the Division. Dr. Stockbridge encouraged the sponsor to submit those data.

Dose Response

Dr. Stockbridge explained that a single dose response study is only favorable when the safety data are unremarkable and the success rate is very high. However, if either of those parameters were not present, the Division is less likely to approve this NDA based on a single dose response study. The sponsor asked Dr. Stockbridge to clarify what he means by a single dose. Dr. Stockbridge replied that the Division would like for Kreussler to explore different doses of Aethoxyskerol. The Division is less concerned about the volume of drug and more interested in the concentration of Aethoxyskerol. He explained that it is unclear if lower concentrations would be effective, safer, and better tolerated. The sponsor answered that in practice physicians/phlebologists will simultaneously treat smaller and larger veins and will often use different concentrations of drug depending on the vein size; for example, the phlebologist will start with 1% Aethoxyskerol for R (reticular) veins, and then proceed to use 0.5% Aethoxyskerol for S (spider) veins. A phlebologist will usually predetermine what concentration and quantity and how many sessions for the patient's leg. Dr. Stockbridge stated that there were not any major objections with the sponsor's strategy as long as the drug product was highly effective and well tolerated, and that the actual usage in the clinical trial will be what goes into the label.

Dr. Stockbridge suggested that Kreussler submit a Special Protocol Assessments (SPA) for their revised protocol. He explained that the Division will review the SPA within 45 days of receipt and will provide a written response that is usually a binding agreement between the sponsor and the Division. The sponsor asked if it will be sufficient to only submit the final study results or will it have to resubmit all integrated safety and efficacy data (NDA Section 8) that had been originally submitted to the NDA. Dr. Stockbridge agreed that the sponsor could just submit the final results.

Sermon 12.2.05
U 12.2.05
Stockbridge 12.2.05

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/s/

Alisea Sermon
12/7/2005 03:34:12 PM

Norman Stockbridge
12/7/2005 04:14:33 PM

Teleconference Meeting Confirmation

Application:	NDA 21-201
Drug:	Aethoxyskerol
Sponsor:	Chemische Fabrik Kreussler & Co., GmbH c/o INC Research
Date Requested:	November 2, 2005
Sponsor Notified:	November 4, 2005
Confirmation Emailed:	November 14, 2005
Meeting Type:	Guidance
Classification:	C
Purpose:	To discuss Kreussler's proposal for a new clinical trial
Meeting Date:	**November 30, 2005**
Meeting Time:	**10:00-11:00am E.S.T.**
Location:	**Teleconference**

FDA Attendees:

Norman Stockbridge, M.D., Ph.D.	Acting Director
Khin Maung U, M.D.	Medical Officer
Alisea Sermon, Pharm.D.	Regulatory Health Project Manager

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/s/

Alisea Sermon
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Meeting Minutes

Meeting Date:	May 18, 2005
Type of Meeting:	Guidance
Classification:	Type C
NDA Application:	NDA 21-201
Drug:	Aethoxysklerol (pilidocanol)
Sponsor:	Chemische Fabrik Kreussler & Co., GmbH c/o INC Research
Meeting Request Date:	April 12, 2005
Confirmation Fax Date:	April 14, 2005
Briefing Package Received:	April 29, 2005
Meeting Location:	Division of Cardio-Renal Drug Products Woodmont Office Complex 2, HFD-110 Fifth Floor, Conference Room "F" 1451 Rockville Pike Rockville, MD 20852
Meeting Chair:	Norman Stockbridge, M.D., Ph.D.
Meeting Recorder:	Alisea Sermon, Pharm.D.

Attendees:

FDA

Norman Stockbridge, M.D., Ph.D.	Acting Director, HFD-110
Abraham Karkowsky, M.D., Ph.D.	Acting Deputy Division Director, HFD-110
Thomas Marciniak, M.D.	Team Leader, Medical Officer, HFD-110
James Hung, Ph.D.	Team Leader, Statistician, HFD-710
Kasturi Srinivasachar, Ph.D.	Team Leader, Chemistry, HFD-810
Robert Kumi, Ph.D.	Clinical Pharmacology & Biopharmaceutics, HFD-860
Alisea Sermon, Pharm.D.	Senior Regulatory Health Project Manager, HFD-110
Brenda Carr, M.D.	Medical Officer, HFD-540
Brenda Vaughan, M.D.	Medical Officer, HFD-540
Steve Hathaway, Ph.D.	Chemist, HFD-540
Roy Blay	Regulatory Affairs, DSI, HFD-47
Sharon Gershon	Regulatory Affairs, DSI, HFD-47
Lei Zhang, Ph.D.	Clinical Pharmacology & Biopharmaceutics, HFD-880
Steven Thomson, Ph.D.	Biostatistician, HFD-725
Frank Cross, M.A.	Senior Regulatory Health Project Manager, HFD-540
Marilyn Pitts	Drug Safety Evaluator, ODS, HFD-430

Chemische Fabrik Kreussler

Stephan Travers, LLD	President, Kreussler
Howard Smith	Vice President, Regulatory Services, INC Research
Joachim Otto, Ph.D.	Director, Medical-Scientific Department, Kreussler
(b) (4)	Regulatory Consultant
(b) (4)	Clinical Professor, Department of Dermatology, (b) (4)
	(b) (4) Clinical Consultant

Background

The application was transferred from the Division of Dermatologic and Dental Drug Products to the Division of Cardio-Renal Drug Products in March 2005. The sponsor received a Not Approvable letter dated August 2, 2004 that summarized outstanding deficiencies for Chemistry, Manufacturing and Controls (CMC), CMC Microbiology, Clinical (Efficacy & Safety), Biostatistics and Clinical Pharmacology and Biopharmaceutics.

Meeting

After introductions, the sponsor asked if the meeting could begin with a discussion of the pharmacokinetic issues. Dr. Stockbridge stated that he had not reviewed in detail all of the pharmacokinetic (PK) data and the Division's recommendation is based on a briefing provided by reviewers from the Division of Dermatologic and Dental Drug Products. He stated that he was unsure if the newer PK data will be helpful because it seems to have a smaller number of subjects and not all of those appear to be evaluable. He explained that PK data can be obtained from the pending clinical trial to address outstanding PK concerns.

There was a discussion about the OHIO study and if that data could be used as the pivotal study. Dr. Stockbridge stated that although the Division of Scientific Investigations (DSI) had serious audit concerns with some of the other centers, the OHIO center seemed to have fewer problems and is more likely to inform on efficacy. The information that the OHIO study provides will not be enough for a pivotal study, but it will provide some additional benefit to the clinical portion of the application. Dr. Stockbridge informed the sponsor that they will have to complete another clinical study and advised not to replicate the OHIO study results.

Dr. Stockbridge inquired about the ASK 97-01-00 Japanese study and if it was sponsored by Kreussler. The sponsor replied that the study was conducted with their Japanese partners using Aethoxyskerol, however it was completed at a later time. Dr. Stockbridge asked if the sponsor believed that the Japanese study would survive a DSI audit. The sponsor replied that they did not think their Japanese partners will grant an audit. Dr. Stockbridge responded that the Japanese study will be completely excluded if an audit is not allowed. The sponsor stated that they understood the Division's position.

Dr. Stockbridge asked if ASK-94-002 and ASK-96-001 were open-label studies. The sponsor replied yes. Dr. Stockbridge stated that those studies will provide very little benefit in respect to efficacy and asked if there were any other studies available. The sponsor stated that there is a large Australian study available, but it is also an open label trial. It is a use study with systematic data collection that did not screen for DVTs. The Division asked if the sponsor could ascertain the durability of effects

Aethoxyskerol could achieve. The sponsor stated that they were unsure and would follow-up with the Division. The Division asked if the sponsor could describe the benefits of the Australian study. The sponsor answered that the study has a strong safety profile and excellent clinical efficacy. DVTs were not screened in this study because in the past, it was not customary to look for thromboses because once the vein is sclerosed there is not a concern of reoccurrence. The usual practice is to follow-up with patients within 3-6 months to determine if treatment was reversible. The Division asked if the sponsor had access to the Australian safety database. The sponsor replied that they were unsure, but they could provide study protocols and will contact the principal investigators about the safety database.

There was a brief discussion about the dose of Aethoxyskerol and how the sponsor derived the dosing regimen. The sponsor indicated that they arrived at the dosing regimen after reviewing other trials showing clinical efficacy and the lowest safety effect profile.

Dr. Stockbridge stated that the Agency is still interested in long-term safety data, approximately one year which is driven by late appearing safety issues and also provide data showing the durability of treatment effects. The sponsor noted that the standard is usually 3-6 months for any changes to reoccur in vessels and inquired about the need for one year safety data. The Division asked if the sponsor could provide data to support the argument that after treatment with Aethoxyskerol or a similar sclerosant, vessels do not recannulize after 3-6 months. The sponsor responded that there are studies that followed-up to 3 months; however there have not been reports to support that argument.

Dr. Stockbridge stated that the endpoints that the sponsor will provide is much different than what the Division is accustomed to receiving. The Division most often looks at mortality and symptomatic claims. He informed the sponsor that the Division expects to receive robust clinical data with a good safety program and will not entertain the idea of negotiating the safety expectations. The sponsor responded that they understood the Division's position, but they continue to struggle with the safety expectations because this product has been on the market for years in other countries. Why now is there a concern for such an extensive amount of safety data and where is the alarm coming from? The sponsor further stated that although they are not opposed to completing another study, they have completed a long literature search and found no history of the safety concerns associated with Aethoxyskerol, such as cardiac arrhythmias. Dr. Stockbridge responded that part of the problem with relying on post marketing data is not having the confidence that an event will be reported. There is not enough data in a controlled setting that can rule out safety events. The sponsor asked why there are safety concerns for Aethoxyskerol and not Sotradecol which is another sclerosing agent (approved by the Agency as an ANDA in November 2004). The Division responded that if there is a generic product that was approved based on a drug that was approved in 1946; the Agency does not have the authority to require additional safety data from the generic product. However, when there are new active ingredients, in respect to scerlosing agents, the Agency has the authority to increase its standards for safety and efficacy so that it can learn more about these agents.

Ms. Pitts (Office of Drug Safety) raised some concern about 5 reports of deaths world-wide that were associated with Aethoxyskerol. The sponsor stated that they were unaware of those reports and if Kreussler were informed of any such events it would have immediately notified the Agency. There was also a discussion about the sponsor's results having a high incidence of superficial vein thrombosis. The sponsor stated that superficial vein thrombosis was used as a description for small-vessel sclerotherapy. The sponsor further stated that it was their mistake to use the term "superficial vein thrombosis". The

Division stated that based on such high incidence of thrombosis the sponsor should have screened for DVTs. The Division also emphasized that any study having an incidence(s) of pulmonary embolism will be completely unacceptable based on the size of the safety database. The sponsor stated that they understood the Division's position.

Dr. Stockbridge recommended that the sponsor complete a three arm study which will include an argument about dose. He mentioned that there are set ICH guidelines that the Division has to follow regardless of clinical benefit (e.g., enrollment of 1,500 patients). The sponsor replied that having an enrollment of 1,500 patients would not apply to their product because it would not be indicated for chronic use and asked that the Division bear in mind that Kreussler is a small business. Dr. Stockbridge stated that the standards for approval are not based on a company's resources. The sponsor noted that they would not be able to start a trial of this sort until the fall because during the summer months women are less prone to have this type of procedure. The Division stated that they understood the sponsor concerns and the fall season seemed like the appropriate time to begin because of the length of time it may take to get through IRB, etc. The Division also encouraged the sponsor to determine if their product can be used for an additional clinical benefit besides cosmecies (e.g., decrease in pain) and it would be willing to have further discussions about a trial to address that benefit.

The sponsor discussed the idea of initially seeking approval of only the .5% and 1% concentrations of Aethoxyskerol (b) (4) (b) (4). (b) (4)
Dr. Stockbridge asked if the sponsor was suggesting using the 3% data as a way to assure safety. The sponsor responded yes (b) (4) The Division asked how their product will be packaged. The sponsor replied that it is a ready to use package that does not require dilution. The Division responded that the sponsor's proposal will be considered and requested that they submit this idea as part of their argument about dosing of Aethoxyskerol. The sponsor agreed.

There was a brief discussion about the type of clinical trial the Division would require. Dr. Stockbridge advised the sponsor to include a large number of centers in their new trial that will provide robustness of clinical results. Based on the earlier discussion, the Division may consider short term data and while under review the sponsor is still expected to collect long-term safety data. He also stated that if there is a large loss of follow-up, the sponsor is expected to convince the Division that it is not because something bad happened to those patients. It may be a challenge because patients who did not receive a good outcome may not be motivated to follow up. He suggested seeking patients who visit their vascular surgeon regularly. The sponsor stated that they will consider the Division's advice and will determine the best approach.

The sponsor asked the Division to define the appropriate number of enrollment sites. The sponsor expressed that there is some concern with finding a large number of centers because of the DVT screening requirement. The Division responded that patients should not be enrolled in cites that can not monitor for DVTs. The Division also advised against having a p value of (b) (4) Dr. Stockbridge strongly recommended having a p value well under (b) (4) The Division also stated that the sponsor will need another 1,000 patients enrolled in the new study. The sponsor stated that enrolling 1,000 patients is a huge issue for Kreussler. Dr. Stockbridge stated that the final number of enrollees did not have to be settled during the meeting. He also briefly explained that the third arm is to protect against any findings

of DVTs. The sponsor stated that they are concerned about the recommended design because it will require that they dilute Sotradecol. The Division suggested using the approved dose of Sotradecol and not to dilute the product. The sponsor agreed to use Sotradecol at its approved dose.

In conclusion, Dr. Stockbridge recommended that the sponsor submit a protocol with their proposals (e.g., dosing rationale, PK data, and patient enrollment number) and submit it to the Division as a Special Protocol Assessment. The Division will review the protocol and will send a written response within 45 days of receipt. Dr. Stockbridge also noted that once the study is completed the sponsor will have to submit a complete response to each deficiency cited in the Not Approvable letter dated August 2, 2004. The sponsor stated that they will consider all recommendations and thanked the Agency for their time.

Signature minutes preparer — *{See appended electronic signature page}*
Alisea Sermon, Pharm.D.

Concurrence, Chair — *{See appended electronic signature page}*
Norman Stockbridge, M.D., Ph.D.

Sermon 5/19/05
Kumi ROK 5/24/05
Hung 5/25/05
Vaughn 5/24/05
Marciniak 5/24/05
Stockbridge 6/2/05

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION

US Mail address:
FDA/CDER/HFD-110
5600 Fishers Lane
Rockville, MD 20857

Woodmont II
1451 Rockville Pike
Rockville, MD 20852

Transmitted to FAX Number:	(434) 295-7209
Attention:	Mr. Howard Smith
Company Name:	INC Research
Phone:	(434) 244-5165
Subject:	Meeting Minutes
Date:	6/2/05
Pages including this sheet:	**7**

From: **Alisea Sermon**
Phone: **301-594-5334**
Fax: **301-594-5494**

Please let me know you received this.

Thank you.

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/s/

Alisea Sermon
6/2/05 07:27:23 AM

Alisea Sermon
6/2/05 07:27:23 AM

Norman Stockbridge
6/2/05 08:43:25 AM

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION

US Mail address:
FDA/CDER/HFD-110
5600 Fishers Lane
Rockville, MD 20857

Woodmont II
1451 Rockville Pike
Rockville, MD 20852

Transmitted to FAX Number:	(434) 295-7209
Attention:	**Mr. Howard Smith**
Company Name:	INC Research
Phone:	(434) 244-5165
Subject:	**Meeting Confirmation**
Date:	4/14/05
Pages including this sheet:	3

From: **Alisea Sermon, Pharm.D.**
Phone: **301-594-5334**
Fax: **301-594-5494**

PLEASE LET ME KNOW YOU RECEIVED THIS. THANK YOU!

MEETING NOTIFICATION

Application:	NDA 21-201
Drug:	Aethoxysklerol
Sponsor:	Kreussler Pharmaceuticals c/o INC Research
Date Requested:	April 12, 2005
Sponsor notified:	April 12, 2005
Confirmation Faxed:	April 14, 2005
Meeting Type:	Guidance
Classification:	C
Purpose:	To discuss the development of Aethoxysklerol and any outstanding NDA deficiencies
Meeting date:	**May 18, 2005**
Meeting Time:	**1:00-2:30pm**
Location:	Division of Cardio-Renal Drug Products Woodmont Office Complex 2 Third Floor, Conference Room "C" 1451 Rockville Pike Rockville, MD 20852

List of FDA Attendees:

Norman Stockbridge, M.D., Ph.D.	Acting Director, HFD-110
Abraham Karkowsky, M.D., Ph.D.	Acting Deputy Director, HFD-110
Thomas Marciniak, M.D.	Team Leader, Medical Officer, HFD-110
Jonathan Wilkin, M.D.	Team Leader, Medical Officer, HFD-540
Brenda Carr, M.D.	Medical Officer, HFD-540
Brenda Vaughan, M.D.	Medical Officer, HFD-540
Kasturi Srinivasachar, Ph.D.	Team Leader, Chemistry, HFD-810
Albert DeFelice, Ph.D.	Team Leader, Pharmacology, HFD-110
Charles Resnick, Ph.D.	Team Leader, Pharmacology, HFD-110
William Link, Ph.D.	Pharmacologist, HFD-110
Lei Zhang, Ph.D.	Biopharmaceutics, HFD-880
Raman Baweja, Ph.D.	Team Leader, Biopharmaceutics, HFD-860
Patrick Marroum, Ph.D.	Team Leader, Clinical Pharmacology & Biopharmaceutics, HFD-860
Marilyn Pitts, Pharm.D.	Drug Safety Evaluator, HFD-430
Alisea Sermon, Pharm.D.	Regulatory Health Project Manager, HFD-110

Please send 15 copies of the briefing package no later than May 2, 2005

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/s/

Alisea Sermon
4/14/05 10:46:30 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Division of Dermatologic and Dental Drug Products
HFD-540

FROM (*Name, Office/Division, and Phone Number of Requestor)*:
Alisea Sermon, HFD-110, Division of Cardio-Renal
(301) 594-5334

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
4/14/05	35,139	21-201	Meeting Request	4/12/2005

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Aethoxysklerol	S	Sclerosing Agent	5/18/2005

NAME OF FIRM: Kreussler Pharmaceuticals
c/o INC Research

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 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: Guidance Meeting on May 18, 2005 with INC Research regarding the above NDA

Internal Meeting 12-1:00pm
Meeting w/ Firm 1:00-2:30pm

SIGNATURE OF REQUESTOR

METHOD OF DELIVERY (Check one)
☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

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/s/

Alisea Sermon

4/14/05 10:52:39 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-201

Chemische Fabrik Kreussler & Co., GmbH
c/o INC Research
Attention: Howard M. Smith
Senior Director, Regulatory Operations & Medical Writing
675 Peter Jefferson Parkway
Suite 120
Charlottesville, VA 22911

Dear Mr. Smith:

Please refer to your new drug application (NDA) dated September 29, 2003, received October 2, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Aethoxysklerol (polidocanol) Injectable, 0.5%, 1%, (b) (4)

We also refer to the meeting between representatives of your firm and the FDA on February 10, 2005. The purpose of the meeting was to discuss the Not Approvable Letter for this NDA.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call Frank H. Cross, Jr., M.A., MT (ASCP), CDR, Senior Regulatory Management Officer, at (301) 827-2020.

Sincerely,

{See appended electronic signature page}

Jonathan K. Wilkin, M.D.
Division Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure

Meeting Date: February 10, 2005 Time: 10:30 a.m.- 12:00 p.m. Location: N225
Meeting ID# 14629

NDA 21-201, Aethoxysklerol (polidocanol) Injectable, 0.5%, 1%, (b) (4)

Indication: Treatment of varicose veins of the lower extremities

Applicant: Inc. Research

Meeting Objective: Discussion of Not Approvable Letter

Meeting Chair: Jonathan K. Wilkin, M.D., Division Director, M.D., DDDDP, HFD-540

Meeting Recorder (CSO/Project Manager): Frank H. Cross, Jr., M.A., CDR

FDA Attendees, titles and offices:

Jonathan K. Wilkin, M.D., Division Director, M.D., DDDDP, HFD-540
Stanka Kukich, M.D., Deputy Division Director, DDDDP, HFD-540
Jonca Bull, M.D., Office Director, Office Director, ODEV, HFD-105
Ramesh Sood, Ph.D., Chemistry Team Leader, DNDCIII, HFD-830
Steve Hathaway, Ph.D., Chemistry Reviewer, DNDCIII, HFD-830
Raman Baweja, Ph.D., Clinical Pharmacology/Biopharmaceutics Team Leader, DPEIII, HFD-880
Lei Zhang, Ph.D., Clinical Pharmacology/Biopharmaceutics Reviewer, DPEIII, HFD-880
Markham C. Luke, M.D., Ph.D., Clinical Team Leader, DDDDP, HFD-540
Brenda Carr, M.D., Medical Officer, DDDDP, HFD-540
Brenda Vaughan, M.D., Medical Officer, DDDDP, HFD-540
Mohamed Alosh, Ph.D., Biostatistics Team Leader, DBIII, HFD-725
Steve Thomson, Biostatistics Reviewer, DBIII, HFD-725
Roy Blay, Ph.D., Director, Regulatory Review Officer, Division of Scientific Investigations, HFD-48
Jose Javier Tavarez-Pagan, Regulatory Review Officer, Division of Scientific Investigations, HFD-48
C.T. Viswanathan, Ph.D., Associate Director, Division of Scientific Investigations, HFD-48
Frank H. Cross, M.A., CDR, Senior Regulatory Management Officer, DDDDP, HFD-540

Applicant Attendees, titles and offices:

Stephen Travers, LLD, President, Kreussler Pharma
Joachim Otto, Ph.D., Director, Medical-Scientific Department, Kreussler Pharma
Howard Smith, Vice President, Regulatory Service and U.S., Representative for Kreussler
Paul Cowden, Vice President, Business Development and Scientific Regulatory Affairs, BSN-Jobst
Angela Pereira, Manager, Regulatory Affairs, BSN-Jobst
(b) (4), J.D., Regulatory Consultant, (b) (4).
(b) (4)., FACP, FAACS, Clinical Professor, Department of Dermatology, (b) (4)
(b) (4); (b) (4), Clinical Consultant

With reference to the Applicant's January 11, and 28, 2005, Meeting Request/Briefing Package and List of Meeting Attendees, respectively, the following discussion took place:

Chemistry, Manufacturing and Controls (CMC) and CMC Microbiology:

The Agency reiterated the CMC Microbiology deficiencies from the Agency's August 2, 2004 Not Approvable Letter:

The applicant acknowledged that they would address the CMC Microbiology Not Approvable deficiencies in their resubmission.

Clinical:

The sponsor introduced the discussion and opened with a historical evaluation of this application. The extended period between the initiation of the IND and the completion of the studies as well as the prolonged interaction after completion of the studies with the Agency was noted. The Agency expressed agreement that the prolonged interaction and regulatory history was tortuous, however, the Agency stressed that the *a priori* statistical plan is most relevant and provides the soundest scientific basis for evaluation of studies.

The sponsor expressed concern regarding the approval of the ANDA for Sotradecol due to its impact on its own product. The Agency noted the differences in informational needs for ANDAs and NDAs. It was discussed that Aethoxysklerol is a New Molecular Entity and not eligible for an Abbreviated New Drug Application.

The Agency stated that the single-center OHIO study, which was previously submitted as a pivotal study, cannot be used as a pivotal study in future summaries, because the sponsor failed to achieve success with its *a priori* designated endpoints. It was discussed that the OHIO study failed to establish superiority for the dichotomized Complete Disappearance of Varicosities efficacy endpoint or Disappearance of Varicosities on a 5-point scale when Aethoxysklerol is compared to diluted Sotradecol (STS). In addition, non-inferiority was not established for the dichotomized Complete Disappearance of Varicosities efficacy endpoint. See also Biostatistical Comments below.

Studies ASK-94-001 & ASK-94-002 will not satisfy efficacy concerns. Both Studies (ASK-94-001 & ASK-94-002), conducted solely in Japan, were dose-finding studies and were previously reviewed under the NDA in support of safety. It is not clear at this time that the data from these studies could be supportive of efficacy; however, it is apparent that these studies would not suffice as pivotal studies. The sponsor was referred to ICH E5 (Ethnic Factors in the Acceptability of Foreign Clinical Data) Guidance document. Please refer also to Biostatistical Comments below.

In addition, it was discussed that the Not Approvable Letter specified two studies were needed. However, one study could suffice if the informational pieces are robust. The sponsor will submit the protocol for the one study for Agency review and agreement prior to conduct. It was agreed that the sponsor could request a Guidance Meeting to discuss a complete protocol including statistical methodology and then potentially qualify for a Special Protocol Assessment.

With regard to a new clinical protocol, a complete protocol would need to be reviewed by the Agency prior to starting.

It was discussed that a demonstration of durability of response up to one year is needed for the initial submission, especially for the larger veins. Reference was made to the August 2, 2004, Not Approvable Letter.

Discussion Regarding Safety:

The sponsor indicated that they did not have as much concern about safety due to the significant historical use in other countries and of unapproved polidocanol in the United States. It was proposed that the emphasis should, instead, be on efficacy.

The Agency informed the sponsor that, contrary to their viewpoint, the safety of this drug product is important and would need to be evaluated in a clinical study prospectively.

Safety procedures in the recommended new clinical studies should include specific plans for assessment for deep vein thrombosis (DVT). No unequivocal conclusions can be made regarding the occurrence of DVT in the sponsor's previously conducted trials, as adequate post-treatment assessments for DVT were not conducted. Since DVT (and emboli) can be clinically silent, their presence could go undetected if the post-treatment assessment is limited to a history and/or physical examination. Post-treatment duplex ultrasound is suggested as a reasonable approach to assessing for DVT post-sclerotherapy, and all study procedures should be performed by properly-trained personnel. The sponsor was reminded that the August 2, 2004, Not Approvable Letter also included other recommendations regarding safety monitoring that should be addressed in any proposed study.

It was discussed that the August 2, 2004, Not Approvable letter has additional items that need to be addressed, including the need for a pharmacokinetic *in vivo* bioavailability study and Chemistry, Manufacturing and Control Microbiology issues regarding product sterility. The sponsor agreed to this.

Biostatistics:

1. It was the sponsor's position that the OHIO study established the non-inferiority with respect to Sotradecol. In response the Agency stated that the sponsor's conclusion was not warranted since:
    a. The study was designed and powered for a superiority claim and not a non-inferiority claim. Previous Agency comments about non-inferiority were intended to be helpful as a supportive analysis, but not as a replacement of the primary analysis pre-specified in the protocol. Furthermore, the sponsor's analysis for non-inferiority was carried out long after completion of the study and unblinding the data.

    b. For non-inferiority comparisons efficacy for the reference listed drug products needs to be known so that selection of a non-inferiority margin excludes the possibility of vehicle response. However, this is not the case for Sotradecol as no well-controlled trial was conducted to estimate the treatment effect. In addition, Sotradecol was diluted in the trial and consequently its efficacy might not be different from placebo.

c. No placebo arm was included in the Study to estimate treatment effect for the Sotredecol or Aethoxysklerol.

2. The sponsor stated that they submitted results from two clinical trials conducted in Japan. The Agency agreed that such studies, depending upon their review might be used as supportive studies in future submissions.

3. In response to the sponsor's request on how to address the Agency comments in the August 2, 2004, Not Approvable Letter, the Agency stated that the sponsor should conduct either two studies or one robust study which should be powered to achieve statistical significance much below the (b) (4) level. The Agency also recommended that the sponsor should refer to the FDA Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products concerning the requirements for a single study submission, and the ICH E9 Statistical Principles for Clinical Trials.

Division of Scientific Inspections (Clinical Pharmacology and Biopharmaceutics)

Our review of the Applicant's response to inspectional FDA Form 483 items does not change the non-acceptability of the data that was originally transmitted to the Agency. The applicant is invited to submit its draft clinical pharmacokinetics protocol and statistical analysis plan to the Agency for review and comment prior to study initiation.

The meeting ended amicably.

Signature, minutes preparer: _____

Concurrence Chair (or designated signatory): _____

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/s/

Jonathan Wilkin
3/9/05 04:55:33 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-201

INC Research
Attention: Howard M. Smith
Vice President, Regulatory Services
675 Peter Jefferson Parkway
Suite 120
Charlottsville, VA 22911

Dear Mr. Smith:

We received your December 3, 2004 correspondence requesting a Type A meeting to discuss the issues identified in our August 2, 2004 Not-Approvable Letter for Aethoxysklerol.

Your meeting has been given our earliest availability, and is scheduled as follows:

Date of Meeting:	Thursday, February 10, 2005
Time:	10:30 PM-11:30 AM
Location:	9201 Corporate Blvd., Rockville, MD 20850

Please provide the background information at least a month prior to the meeting. Submit the original copy to your NDA, and 15 copies, each marked "DESK COPY", directly to Sandy Childs at the above address. If we do not receive it by January 10, 2004, we may have to reschedule.

If you have any questions, call Sandy Childs, Consumer Safety Technician, at 301-827-2061.

Sincerely,

{See appended electronic signature page}
Mary Jean Kozma-Fornaro
Supervisor, Project Management Staff
Division of Dermatologic & Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/s/

Suzanne Childs
12/16/04 12:29:05 PM
Signed for Mary Jean Kozma-Fornaro

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-201

Chemische Fabrik Kreussler & Co., GmbH
c/o INC Research
Attention: Howard M. Smith
Senior Director, Regulatory Operations & Medical Writing
675 Peter Jefferson Parkway
Suite 120
Charlottesville, VA 22911

Dear Mr. Smith:

Please refer to your new drug application (NDA) dated September 29, 2003, received October 2, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Aethoxysklerol (polidocanol) Injectable, 0.5%, 1%, (b) (4)

We also refer to the meeting between representatives of your firm and the FDA on October 13, 2004. The purpose of the meeting was to discuss the Not Approvable Letter for this NDA.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call Frank H. Cross, Jr., M.A., MT (ASCP), CDR, Senior Regulatory Management Officer, at (301) 827-2020.

Sincerely,

{See appended electronic signature page}

Stanka Kukich, M.D.
Deputy Division Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure

Meeting Date: October 13, 2004 Time: 1:30 p.m. Location: N225
Meeting ID# 13912

NDA 21-201, Aethoxysklerol (polidocanol) Injectable, 0.5%, 1%, (b) (4)

Indication: Treatment of varicose veins of the lower extremities

Applicant: Inc. Research

Meeting Objective: Discussion of Not Approvable Letter

Meeting Chair: Stanka Kukich, M.D.

Meeting Recorder (CSO/Project Manager): Frank H. Cross, Jr., M.A., CDR

FDA Attendees, titles and offices:

Stanka Kukich, M.D., Deputy Division Director, DDDDP, HFD-540
Brian Harvey, M.D., Deputy Office Director, ODEV, HFD-105
Shaw Chen, M.D., Associate Director for Special Product Review, Botanical Review Team, HFD-105
Terri Rumble, Associate Director for Regulatory Affairs, ODEV, HFD-105
Ramesh Sood, Ph.D., Chemistry Team Leader, DNDCIII, HFD-830
Steve Hathaway, Ph.D., Chemistry Reviewer, DNDCIII, HFD-830
Stephen Langille, Ph.D., CMC Microbiology Reviewer, HFD-170
Raman Baweja, Ph.D., Clinical Pharmacology/Biopharmaceutics Team Leader, DPEIII, HFD-880
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Brenda Carr, M.D., Medical Officer, DDDDP, HFD-540
Brenda Vaughan, M.D., Medical Officer, DDDDP, HFD-540
Mohamed Alosh, Ph.D., Biostatistics Team Leader, DBIII, HFD-725
Steve Thomson, Biostatistics Reviewer, DBIII, HFD-725
Roy Blay, Ph.D., Director, Regulatory Review Officer, Division of Scientific Investigations, HFD-48
C.T. Viswanathan, Ph.D., Associate Director, Division of Scientific Investigations, HFD-48
Margo Owens, Regulatory Project Manager, DDDDP, HFD-540
Frank H. Cross, M.A., CDR, Senior Regulatory Management Officer, DDDDP, HFD-540

Applicant Attendees, titles and offices:

Stephen Travers, LLD, President, Kreussler Pharma
Joachim Otto, Ph.D., Director, Medical-Scientific Department, Kreussler Pharma
Howard Smith, Vice President, Regulatory Service and U.S., Representative for Kreussler
Rajagopalan Srinivasan, Ph.D., Vice President, Biostatistics
Paul Cowden, Vice President, Business Development and Scientific Regulatory Affairs, BSN-Jobst
(b) (4) Ph.D., DABT, ATS, (b) (4), Regulatory Consultant
(b) (4), Ph.D., RAC., (b) (4), Regulatory Consultant
(b) (4) M.D., FACP, FAACS, Clinical Professor, Department of Dermatology, (b) (4)
(b) (4) Clinical Consultant

(b) (4), M.D., FACEP, FAAEM, Clinical Associate Professor, Department of Emergency Medicine, (b) (4)

, Clinical Consultant

With reference to the Applicant's September 20, 2004, Meeting Request/Briefing Package, the following discussion took place:

Agency:

The Agency reiterated the contents of the August 2, 2004, Not Approvable Letter for NDA 21-201, Aethoxysklerol (polidocanol) Injectable, 0.5%, 1%, (b) (4) The purpose of the meeting was only to clarify the Not Approvable Letter and not to come to agreement regarding the specific issues listed in the Not Approvable Letter. The Applicant was reminded to submit a complete response to the Not Approvable Letter upon completion of all needed studies.

Applicant:

The Applicant presented a brief history of the application and indicated there are no currently approved sclerosing agents in the U.S., and that there is worldwide clinical experience in the use of polidocanol.

Agency:

1. Even though polidocanol is widely used as a sclerosing agent, the New Drug Application did not provide substantial evidence of efficacy for polidocanol. Polidocanol was not superior to Sotradecol; the comparator that was approved in 1946, and for which no controlled clinical efficacy data exists demonstrating the treatment effect. Therefore a comparative study should be a demonstration of superiority rather than non-inferiority. Adequate and well-controlled clinical trials are needed to support the efficacy of polidocanol.

   Regarding the quality and integrity of the efficacy data, the Agency made reference to the sponsor's proposal to address these issues by reanalyzing the data after omitting several subjects from the database (page 2 of the Sponsor's cover letter of the briefing package). The Agency pointed out that the integrity of the data as a whole can not be resolved by this after the fact approach and the Agency concerns about these issues still hold.

2. Concerning the DSI inspection results, protocols should be followed as written.

3. No unequivocal conclusions can be made regarding the occurrence of DVT in the Applicant's trials, since adequate post-treatment assessments for DVTs were not conducted. Because DVTs (and emboli) can be clinically silent, their presence could go undetected if the post-treatment assessment is limited to a physical examination. The Applicant acknowledged this at the meeting.

Applicant:

Complete disappearance of varicosities (89%) was the endpoint which was considered for evaluating efficacy. A response rate of 80% – 90% was observed.

The Applicant queried the Agency for the rationale for selection of at least 300 subjects for the safety evaluation, to which the Agency referred the Applicant to ICH Guidance E1A The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-term Treatment of Non-Life-Threatening Conditions, since this drug could be used repeatedly on a chronic basis. The Agency suggested that some of the safety data from the current safety database might be considered to be supportive.

Agency:

The Agency is willing to work with the Applicant on future protocol designs to satisfy the Not Approvability Issues cited in the aforementioned Not Approvable Letter and should submit study protocol(s) for Agency review and comment prior to study initiation.

The meeting ended amicably.

Addendum:

Chemistry, Manufacturing and Controls Microbiology:

The Applicant should submit its responses to the CMC Microbiology deficiencies as an amendment to the original application, NDA 21-201.

Division of Scientific Inspections (Clinical Pharmacology and Biopharmaceutics)

Our review of the Applicant's response to inspectional FDA Form 483 items does not change the non-acceptability of the data that was originally transmitted to the Division.

Clinical Pharmacology and Biopharmaceutics:

The Applicant is invited to submit its draft pK protocol to the Agency for review and comment prior to study initiation.

Signature, minutes preparer: _____

Concurrence Chair (or designated signatory): _____

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/s/

Stanka Kukich
11/9/04 01:29:38 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-201

INC Research
Attention: Howard M. Smith
Vice President, Regulatory Services
675 Peter Jefferson Parkway
Suite 120
Charlottsville, VA 22911

Dear Mr. Smith:

We received your August 11, 2004 correspondence requesting a Type A meeting to discuss the issues identified in our August 2, 2004 Not-Approvable Letter for Aethoxysklerol.

The meeting is granted and is scheduled as follows:

Date Requested:	Week of October 11, 2004
Date of Meeting:	Wednesday, October 13, 2004
Time:	1:30 PM-2:30 PM
Location:	9201 Corporate Blvd., Rockville, MD 20850

Please provide the background information at least a month prior to the meeting. Submit the original copy to your NDA, and 15 copies, each marked "DESK COPY", directly to Sandy Childs at the above address. If we do not receive it by September 15 2004, we may have to reschedule.

If you have any questions, call Sandy Childs, Consumer Safety Technician, at 301-827-2061.

Sincerely,

{See appended electronic signature page}
Mary Jean Kozma-Fornaro
Supervisor, Project Management Staff
Division of Dermatologic & Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Suzanne Childs
8/23/04 08:28:40 AM
Signed for Mary Jean Kozma-Fornaro

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V

FACSIMILE TRANSMITTAL SHEET

DATE: April 19, 2004

To: Howard M. Smith, Senior Director Regulatory Operations & Medical Writing	**From:** Lea Carrington Regulatory Project Manager
Company: Chemische Fabrik Kreussler & Co. c/o INC Research	Division of Dermatologic & Dental Drug Products
Fax number: (434) 295-7209	**Fax number:** (301) 827-2091 or 2075
Phone number: (434) 244-5165	**Phone number:** (301) 827-2020

Subject: NDA 21-201: Information Request

Total no. of pages including cover:

Comments: Information Request: Clinical

Document to be mailed: **" YES** **☑ NO**

FDA Fax Memorandum

Date: April 19, 2004

To: Howard M. Smith, Senior Director
Regulatory Operations & Medical Writing

Applicant: Chemische Fabrik Kreussler & Co.
c/o INC Research

Subject: NDA 21-201 Information Request

Dear Howard,

We reference the Agency's, April 16, 2004, telephone request that you provide copies of all Case Report Forms (CRFs), sorted by site, for the pivotal studies of New Drug Application (NDA) 21-201, Aethoxysklerol (polidocanol) 0.5%, 1%, (b) (4)
Please provide the requested information by making an official submission to your NDA via the Central Document Room.

The Agency believes the details on techniques used for sclerotherapy in the pivotal studies are important for the assessment for safety and efficacy and would appreciate a timely response to the following Clinical Request for Information:

Clinical

1. The description of the sclerotherapy techniques used at each study site submitted to the Agency (N-000(BZ) correspondence date 03-25-04, received 03-29-04) is too general with only minor variations noted in Attachment 4. More detailed descriptions of the sclerotherapy techniques used are needed.

2. Please provide, in tabular form, the sclerotherapy techniques used and the specific patients for which they were used. In the table, please include information to address the items listed below, along with any other pertinent details regarding technique:

   a. Was perivascular technique used for the ≤1 mm vein size? If so, please describe the technique sorted per patient by: study group assignment, efficacy outcome, and AEs. As per the protocol (Vol. 35 of 50, pg. 2414), at a concentration of 0.5%, Aethoxyskerol may be injected perivascularly.

   b. Did any investigators "foam" the study drug prior to injection? If so, please describe the technique sorted per patient by: study group assignment, efficacy outcome, and AEs.

c. Was ligation (proximal or other) performed for treatment of larger veins prior to sclerotherapy and compression?

d. Describe the type of compression used for each patient per vein size, study group assignment, efficacy outcome, and AEs.

e. Re: ASK 94-002 and ASK 96-001, ISS Table 8.H.1 "Studies Used to Determine Safety," provides the number of subjects who received a specified concentration of Aethoxysklerol, but does not give a breakdown of subjects according to vessel size diameter, classified as Categories I, II, III. Please provide this breakdown, since there is overlap of categories between the treatment groups, e.g. how many subjects who received the 1% concentration were Category I vs. Category II.

3. Please identify and provide the credentials for the unblinded investigator at each study site.

If you have any questions, please contact me at (301) 827-2020.

Respectfully,

Lea Carrington
Regulatory Project Manager

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/s/

Leonthena Carrington
4/19/04 12:31:43 PM
CSO
Faxed to Applicant 4/19/04.

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V

FACSIMILE TRANSMITTAL SHEET

DATE: April 2, 2004

To: Howard M. Smith, Senior Director Regulatory Operations & Medical Writing	**From:** Lea Carrington Regulatory Project Manager
Company: Chemische Fabrik Kreussler & Co. c/o INC Research	Division of Dermatologic & Dental Drug Products
Fax number: (434) 295-7209	**Fax number:** (301) 827-2091 or 2075
Phone number: (434) 244-5165	**Phone number:** (301) 827-2020

Subject: NDA 21-201: Information Request

Total no. of pages including cover: 3

Comments: Information Request: Clinical

Document to be mailed: • YES ☑ NO

FDA Fax Memorandum

Date: April 2, 2004

To: Howard M. Smith, Senior Director
Regulatory Operations & Medical Writing

Applicant: Chemische Fabrik Kreussler & Co.
c/o INC Research

Subject: NDA 21-201 Information Request

Dear Howard,

The clinical reviewer have requested the following information to facilitate review of New Drug Application (NDA) 21-201, Aethoxysklerol (polidocanol) 0.5%, 1% (b) (4)
To expedite your response, please respond by facsimile in addition to making an official submission to your NDA via the Central Document Room.

Clinical
Please provide the dates of all protocol amendments.

Please submit your response by April 9, 2004. If you have any questions, please contact me at (301) 827-2020.

Respectfully,

Lea Carrington
Regulatory Project Manager

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/s/

Leonthena Carrington
4/2/04 10:40:26 AM
CSO
Faxed to Applicant 4/2/04.

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V

FACSIMILE TRANSMITTAL SHEET

DATE: March 9, 2004

To: Howard M. Smith, Senior Director Regulatory Operations & Medical Writing	**From:** Lea Carrington Regulatory Project Manager
Company: Chemische Fabrik Kreussler & Co. c/o INC Research	Division of Dermatologic & Dental Drug Products
Fax number: (434) 295-7209	**Fax number:** (301) 827-2091 or 2075
Phone number: (434) 244-5165	**Phone number:** (301) 827-2020

Subject: NDA 21-201: Biostatistics clarification

Total no. of pages including cover: 4

Comments: Biostatistics clarification regarding 2/27/04 Information Request.

Document to be mailed: **" YES** **☑ NO**

FDA Fax Memorandum

Date: March 9, 2004

To: Howard M. Smith, Senior Director
Regulatory Operations & Medical Writing

Applicant: Chemische Fabrik Kreussler & Co.
c/o INC Research

Subject: NDA 21-201 Biostatistics clarification to February 27, 2004 Information Request

Dear Howard,

This memo is in response to your March 8, 2004 telephone request for clarification of comment 3 of the Biostatistics section of the Information Request faxed to you on February 27, 2004. For ease of review, I have repeated the Biostatistics information request in bold, followed by FDA clarification.

Biostatistics Question 3:
Data is not available for all subjects. Please explain why data was not taken for all enrolled subjects since, as stated, no one dropped out of the study.

The list below contains the study subjects with missing data as documented in the SAS datasets for NDA 21-201, Aethoxysklerol. Missing data are indicated by a dash or period.

MICA

PT	SAT IS	DIS AP	CLIN	TRT	DIS AP2	CLIN2	STUDY	INV	AGE	HEIGHT	WEIGHT	VEIN	GEND
1112	.	.	.	B	-	-	1	1	35	66	135	1	F
1120	.	.	.	B	-	-	1	1	49	68	125	1	F
1202	.	.	.	A	-	-	1	1	31	69	128	2	F
1225	.	.	.	B	-	-	1	1	48	62	125	2	F
1312	.	4.33333	5.16667	B	Partial a) the majority	Moderate	1	1	29	64	125	3	F
3102	.	1.00000	0.00000	A	Worse than before	Poor	1	3	52	64	126	1	F
3107	.	.	.	A	-	-	1	3	36	67	155	1	F
3201	.	3.00000	3.33333	A	Partial b) the minority	Fair	1	3	44	63	157	2	F
3203	.	.	.	A	-	-	1	3	41	64	120	2	F
3205	.	.	.	A	-	-	1	3	30	67	156	2	F

Ohio

PT	SATIS	DISAP	CLIN	TRT	DISAP2	CLIN2	STUDY	INV	AGE	HEIGHT	WEIGHT	VEIN	GENDER
2101	.	.	.	A	-	-	2	2	40	67.00	171.75	1	F
2103	.	.	.	A	-	-	2	2	26	64.50	157.00	1	F
2106	.	.	.	A	-	-	2	2	53	51.50	134.00	1	F
2116	.	.	.	A	-	-	2	2	38	65.50	133.00	1	F
2201	.	.	.	A	-	-	2	2	37	66.50	132.25	2	F
2204	.	.	.	A	-	-	2	2	45	64.25	161.50	2	F
2217	.	.	.	B	-	-	2	2	25	69.50	152.00	2	F
2238	.	.	.	B	-	-	2	2	39	64.50	156.00	2	F

Please do not hesitate to contact me if you have additional questions.

Respectfully,

Lea Carrington
Regulatory Project Manager

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/s/

Leonthena Carrington
3/9/04 02:39:00 PM
CSO
Faxed to Applicant 3/9/04.

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V

FACSIMILE TRANSMITTAL SHEET

DATE: March 2, 2004

To: Howard M. Smith, Senior Director Regulatory Operations & Medical Writing	**From:** Lea Carrington Regulatory Project Manager
Company: Chemische Fabrik Kreussler & Co. c/o INC Research	Division of Dermatologic & Dental Drug Products
Fax number: (434) 295-7209	**Fax number:** (301) 827-2091 or 2075
Phone number: (434) 244-5165	**Phone number:** (301) 827-2020

Subject: **NDA 21-201: Information Request**

Total no. of pages including cover:

Comments: Information Request: Biopharmaceutics & Draft label

Document to be mailed: • YES ☑ NO

FDA Fax Memorandum

Date: March 2, 2004

To: Howard M. Smith, Senior Director
Regulatory Operations & Medical Writing

Applicant: Chemische Fabrik Kreussler & Co.
c/o INC Research

Subject: NDA 21-201 Information Request

Dear Howard,

Please provide the requested information to facilitate review of New Drug Application (NDA) 21-201, Aethoxysklerol (polidocanol) 0.5%, 1%, (b) (4) To expedite your response, when feasible, please respond by facsimile in addition to making an official submission to your NDA via the Central Document Room.

Biopharm

1. Copies of the individual case report forms (CRFs).
2. Electronic SAS dataset of PK data for PK study ASK-00-01-00.

Regulatory

Please provide a Word document of the draft label identical to the draft labeling submitted September 29, 2003, in the paper copy of the NDA (Vol. 2, Section 2).

Please submit your response within two weeks of receipt of this request. If unable to respond within this time period, please provide justification to extend the date. If you have any questions, please contact me at (301) 827-2020.

Respectfully,

Lea Carrington
Regulatory Project Manager

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/s/

Leonthena Carrington
3/2/04 09:36:50 AM
CSO
Faxed to Applicant 3/2/04.

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V

FACSIMILE TRANSMITTAL SHEET

DATE: February 27, 2004

To: Howard M. Smith, Senior Director Regulatory Operations & Medical Writing	**From:** Lea Carrington Regulatory Project Manager
Company: Chemische Fabrik Kreussler & Co. c/o INC Research	Division of Dermatologic & Dental Drug Products
Fax number: (434) 295-7209	**Fax number:** (301) 827-2091 or 2075
Phone number: (434) 244-5165	**Phone number:** (301) 827-2020

Subject: NDA 21-201: Information Request

Total no. of pages including cover:

Comments: Information Request: Biostatistics/Clinical

Document to be mailed: **" YES** **☑ NO**

FDA Fax Memorandum

Date: February 27, 2004

To: Howard M. Smith, Senior Director
Regulatory Operations & Medical Writing

Applicant: Chemische Fabrik Kreussler & Co.
c/o INC Research

Subject: NDA 21-201 Information Request

Dear Howard,

The clinical and statistical reviewers have requested additional information to facilitate review of New Drug Application (NDA) 21-201, Aethoxysklerol (polidocanol) 0.5%, 1%. (b) (4) To expedite your response, when feasible, please respond by facsimile in addition to making an official submission to your NDA via the Central Document Room.

Biostatistics

1. Please provide SAS data sets with a list of the dates for all photographs taken (i.e. before and after). Include number of treatments per patient and the date of treatment.
2. Please provide data sets with the score of each evaluator in both disappearance of varicosities and level of improvement. (Mean scores have been provided, however, individual scores are needed).
3. Data is not available for all subjects. Please explain why data was not taken for all enrolled subjects since, as stated, no one dropped out of the study.

Clinical

1. Where in the submission are details of the sclerotherapy technique used by the investigator located? Details of the technique were to be described and recorded (Section 8, Vol. 35, pg. 2557). If not present in the NDA, the Applicant is requested to provide detailed sclerotherapy technique per Investigator and provide per patient line listings sorted by Aethoxysklerol and Sotradecol treatment study arms, vein size, and efficacy outcome corresponding to the technique. A written discussion of the most suitable technique and whether these techniques were used uniformly throughout the studies submitted should be provided.

2. According to the original protocol and Amendments 1 and 2 (Vol. 31, section 8, pages 8.469, 8.527, and 8.657; respectively) color photographs were to be taken before, at one month, and four months after the last treatment. When was the protocol amended to exclude photographs at one month? If one month photographs were not excluded prior to study initiation, are any one month photographs available? If so, how many are available?

Please submit your response within two weeks of receipt of this request. If unable to respond within this time period, please provide justification to extend the date. If you have any questions, please contact me at (301) 827-2020.

Respectfully,

Lea Carrington
Regulatory Project Manager

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/s/

Leonthena Carrington
2/27/04 05:16:20 PM
CSO
Faxed to Applicant 2/27/04.

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V

FACSIMILE TRANSMITTAL SHEET

DATE: February 17, 2004

To: Howard M. Smith, Senior Director Regulatory Operations & Medical Writing	**From:** Lea Carrington Regulatory Project Manager
Company: Chemische Fabrik Kreussler & Co. c/o INC Research	Division of Dermatologic & Dental Drug Products
Fax number: (434) 295-7209	**Fax number:** (301) 827-2091 or 2075
Phone number: (434) 244-5165	**Phone number:** (301) 827-2020

Subject: NDA 21-201: Information Request

Total no. of pages including cover:

Comments: Clinical Information Request

Document to be mailed: • •YES ☑ NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 827-2020. Thank you.

FDA Fax Memorandum

Date: February 17, 2004

To: Howard M. Smith, Senior Director
Regulatory Operations & Medical Writing

Applicant: Chemische Fabrik Kreussler & Co.
c/o INC Research

Subject: NDA 21-201 Information Request

Dear Howard,

The clinical reviewers have requested additional information to facilitate review of New Drug Application (NDA) 21-201, Aethoxysklerol (polidocanol) 0.5%, 1%. (b) (4) Please submit the following documentation to the Central Document Room as an official submission to your NDA:

1. A hyperlinked version of the text-accessible electronic documents submitted to the NDA.
2. Post-marketing adverse events for polidocanol-containing products in all countries where the drug is approved.
3. A description of the sclerotherapy technique used by investigators at each study site.

If you have any questions, please contact me at (301) 827-2020.

Respectfully,

Lea Carrington
Regulatory Project Manager

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/s/

Leonthena Carrington
2/17/04 01:06:03 PM
CSO
Faxed to applicant 2/17/04.

Memorandum

DATE: January 27, 2004

TO: Khin Maung U, M.D.
Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

FROM: Lea Carrington, Project Manager, HFD-540

CC: Roy Blay, Ph.D.
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

SUBJECT: **DSI Consult: Request for Clinical Inspections**
NDA 21-201
Aethoxysklerol (polidocanol) Injectable, 0.5%, 1%, (b) (4)
Chemische Fabrik Kreussler c/o INC Research, Inc.

Protocol/Site identification:

The following protocols/sites essential for approval have been identified for inspection. These sites are listed in order of priority.

Indication	Protocol #	Site	# of Subjects
Varicose veins	OHIO/MICA	Southfield, Michigan	41 (38)
Varicose veins	OHIO/MICA	Cincinnati, Ohio	150 (142)
Varicose veins	OHIO/MICA	LaJolla, California	133 (128)

Goal Date for Completion:

We request that the inspections be performed and the Inspection Summary Results provided by **June 1, 2004**. We intend to issue an action letter on this application by **August 2, 2004**.

Should you require any additional information, please contact Lea Carrington, Regulatory Project Manager (Ph: 827-2072).

Concurrence (if necessary):

Medical Team Leader: Markham Luke, M.D., Ph.D.

Medical Reviewers: Brenda Carr, M.D.
Brenda Vaughan, M.D.

Biostat Team Leader: Mohamed Alosh, Ph.D.
Biostat Reviewer: Steve Thomson

Additional information:

Letter Date:	September 29, 2003
Receipt Date:	October 2, 2003
Sponsor:	Chemische Fabrik Kreussler & Co. GmbH
Sponsor Contact:	Howard M. Smith, INC Research, Inc.
Sponsor Contact Phone Number:	434-244-5165
Project Manager:	Lea Carrington
Medical Officers:	Brenda Carr, M.D. & Brenda Vaughan, M.D.
Statistician:	Steve Thomson, Ph.D.
Class:	Sclerosing agent
Indication:	Treatment of varicose veins of the lower extremities
Review:	Standard
Date for Clinical Inspection Summary:	June 1, 2004
Primary Use Fee Goal Date:	Waiver granted
Filing meeting:	November 10, 2003

Distribution: NDA
HFD-45/Division File
HFD-46/Blay

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/s/

Leonthena Carrington
1/27/04 09:28:03 AM

DSI CONSULT: Request for Clinical Inspections

Date: January 22, 2004

To: Roy Blay, GCPB Reviewer/HFD-46
Dr. CT Viswanathan, Associate Director Bioequivalence, HFD-48

From: Ginny Giroux, Regulatory Project Manager, HFD-540

Subject: **Request for Clinical Inspections**
NDA 21-201
Aethoxysklerol (polidocanol) 0.5%, 1%, (b) (4)
Chemische Fabrik Kreussler & Co., GmbH

Protocol/Site Identification:

As discussed with you, the following protocols/sites essential for approval have been identified for inspection. These sites are listed in order of priority.

Indication	Study #	Site (Name and Address)	Number of Subjects
Treatment of varicose veins of the lower extremities	ASK-00-01-00	Department of Dermatology, Sakai Municipal Sakai Hospital, 1-1-1 Minamiyasui-cho, Sakai, 590-0064, Japan **Testing Lab:** (b) (4)	6

**** The study we request for investigation is a PK pivotal study conducted in Japan and the following provides the rationale for our request:**

- **Despite of small numbers of patients in this PK study, this study is a pivotal *in vivo* pk study to support the approval of this NDA.**

- **The drug is an intravenous drug that is intended to treat varicose veins by causing local damage to the endothelium of blood vessels resulting in a closing off of the lumen. Because of the potential for the destruction of otherwise normal vasculature, it is unethical to administer it to healthy volunteers. It is also a dangerous drug to enroll large numbers of patients for the study because of the design nature of this trial, ie. the attempt to attain systemic circulation with a sclerosing agent.**

- **Given the indication, patient population, and the general single use nature of this product, coupled with the small variability in PK of an intravenous drug, it is the Agency's view that PK data from 5 patients will be sufficient. While a more representative US population would be preferable, we have no reason to suspect an ethnic differences in PK for this drug.**

Goal Date for Completion:

We request that the inspections be performed and the Inspection Summary Results be provided by (inspection summary goal date) **June 23, 2004 (labeling day)**. We intend to issue an action letter on this application by (action goal date) **August 2, 2004.**

Should you require any additional information, please contact Lea Carrington at 301-827-2020.

Concurrence: (if necessary)

Lei K Zhang, Ph.D., Pharmacokinetics Reviewer

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/s/

Virginia Giroux

1/23/04 07:41:47 AM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V

FACSIMILE TRANSMITTAL SHEET

DATE: December 19, 2003

To: Howard M. Smith, Senior Director Regulatory Operations & Medical Writing	**From:** Lea Carrington Regulatory Project Manager
Company: Chemische Fabrik Kruessler & Co. c/o INC Research	Division of Dermatologic & Dental Drug Products
Fax number: (434) 295-7209	**Fax number:** (301) 827-2091 or 2075
Phone number: (434) 244-5165	**Phone number:** (301) 827-2020

Subject: NDA 21-201

Total no. of pages including cover:

Comments: Minutes from Biopharm teleconference attached.

Document to be mailed: **" YES** **☑ NO**

MEMO OF FILING MEETING

DATE: **November 24, 2003**

BACKGROUND:
Aethoxysklerol was developed for use as a sclerosing agent and registered for use in Germany in 1967. It reportedly has been used abroad for the treatment of teleangiectasias of the lower limbs in human patients.

NDA 21-201 was originally submitted on October 1, 1999. The application was withdrawn December 1, 1999, due to issues with human pharmacokinetic data. The NDA was resubmitted on September 29, 2003. The filing goal date is December 15, 2003.

ATTENDEES: Jonathan Wilkin, M.D, Jonca Bull, M.D., Terri Rumble, BSN, Markham Luke, M.D., Ph.D., Wilson DeCamp, Ph.D., Mohamed Al Osh, Ph.D., Stanka Kukich, M.D., Michael Albert, M.D., and Mary Jean Kozma-Fornaro in addition to the reviewers listed below.

ASSIGNED REVIEWERS:

Discipline	**Reviewer**	**Review Date**
Medical: (efficacy)	Brenda Vaughan, M.D.	May 1, 2004
Secondary Medical: (safety)	Brenda Carr, M.D.	May 1, 2004
Statistical:	Steve Thomson, Ph.D.	May 1, 2004
Pharmacology:	David Allen, Ph.D.	May 1, 2004
Statistical Pharmacology:		
Chemistry:	Joel S. Hathaway, Ph.D.	May 1, 2004
Environmental Assessment (if needed):		
Biopharmaceutical:	Lei Zhang, Ph.D.	May 1, 2004
Microbiology, sterility:	David Hussong, Ph.D.	May 1, 2004
Microbiology, clinical (for antimicrobial products only):		
DSI:	Gerald Hajarian	
Regulatory Project Management:	Lea Carrington	
Other Consults:		

Per reviewers, are all parts in English or English translation? YES **X** NO
If no, explain:

CLINICAL FILE __**YES**_____ REFUSE TO FILE _____

- Clinical site inspection needed: YES **X** NO
- Advisory Committee Meeting needed? YES, date if known _____ NO
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?
  N/A **X** YES NO

CLINICAL MICROBIOLOGY NA _X_____ FILE _____ REFUSE TO FILE _____

STATISTICS FILE ___X___ REFUSE TO FILE _____

BIOPHARMACEUTICS FILE ___X___ REFUSE TO FILE _____

- Biopharm. inspection needed: YES NO X

PHARMACOLOGY NA _____ FILE ___X___ REFUSE TO FILE _____

- GLP inspection needed: YES NO X

CHEMISTRY FILE ___X___ REFUSE TO FILE _____

- Establishment(s) ready for inspection? YES X NO
- Microbiology N/A X YES NO

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:

_____ The application is unsuitable for filing. Explain why:

___X___ The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

_____ No filing issues have been identified.

___X___ Filing issues to be communicated by Day 74; December 15, 2003.

List (optional):

ACTION ITEMS:

1. Document filing issues will be conveyed to applicant by Day 74, December 15, 2003. The 74-day letter was faxed to the applicant on December 15, 2003.

_____
Regulatory Project Manager, HFD-540

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/s/

Jonathan Wilkin
12/16/03 11:15:11 AM

MEMORANDUM OF TELECON

DATE: December 1, 2003, 1:30 P.M.

APPLICATION NUMBER: NDA 21-201
DRUG PRODUCT: Aethoxysklerol (polidocanol) Injectable 0.5%, 1%, (b) (4)

BETWEEN:

Name:	Howard M. Smith, Senior Director Regulatory Operations & Medical Writing
Phone:	(434) 244-5165
Representing:	INC Research, Inc.

AND

Name:	Division of Dermatologic and Dental Drug Products, HFD-540 Dennis Bashaw, Pharm.D., Team Leader, Pharmacokinetics Lei Zhang, Ph.D., Biopharmaceutics Reviewer Lea Carrington, Regulatory Project Manager

SUBJECT: NDA 21-201

The teleconference was requested by the Biopharmaceutics Reviewer to obtain clarification on the product lot numbers.

The Agency requested that the Applicant provide clarification on the following items:

1. A written statement verifying the assigned numbering for the lots used.
2. Verification that the in process specification for the raw drug substance produced by (b) (4) are the same or improved in the final to-be-marketed dosage form.

The conversation ended amicably.

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/s/

Leonthena Carrington
12/19/03 09:16:35 AM
CSO
Biopharm Tcon 12/1/03.

Dennis Bashaw
12/19/03 02:22:49 PM
BIOPHARMACEUTICS

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/s/

Leonthena Carrington
12/19/03 02:45:47 PM
CSO
Faxed to applicant 12/19/03.

45 DAY MEETING CHECKLIST

FILEABILITY:

On initial overview of the NDA application: **NO**

CLINICAL:

1. **On its face, is the clinical section of the NDA organized in a manner to allow substantive review to begin?** No

2. **Is the clinical section of the NDA indexed and paginated in a manner to allow substantive review to begin?** No; no table of contents for Volumes 35 through Volume 43 (pp. 2292A-5427), contents of which include the individual Clinical Study Reports for the pivotal trials (MICA and OHIO) and data listings.

3. **On its face, is the clinical section of the NDA legible so that substantive review can begin?** Yes

4. **If needed, has the sponsor made an appropriate attempt to determine the most appropriate dosage and schedule for this product (i.e., appropriately designed dose- ranging studies)?** It does not appear that dose-ranging studies were done.

5. **On its face, do there appear to be the requisite number of adequate and well-controlled studies in the application?** No

Application Type: 505(b)(1)

Identification of pivotal trials:

Pivotal Study #1: OHIO (initiation: January 6, 1993; completion: July 26, 1995; Vol. 35, p. 2293)
Page Location: Protocol: Vol. 31, p. 453 **Study Report:** Vol. 35, p. 2293 (dated August 24, 1998)

Is this an adequate multi-centered trial? No; single center (Vol. 35, p.2295)

J. Leonel Villavicencio, M.D. (Prinicipal Investigator; Vol. 31, p. 746)
Uniformed Services University of the Health Sciences
Bethesda, MD

All other investigators were at the Kachelmacher Memorial Clinic, Inc. in Logan, OH (Vol. 31, p.746):

1. Joann Lohr, MD (Coordinating Investigator; study report, Vol. 35, p.2295)
2. John J. Cranley, MD
3. (b) (4)

150 subjects were enrolled, 50 in each treatment arm; the 50 subjects in each group were equally randomized to either Aethoxysklerol (73 subjects) or Sotradecol (69 subjects); no data were collected for 8 subjects; unclear how many subjects were enrolled per investigator.

Study Title: Double-Blind, Prospective, Randomized, Comparative Trial Between Aethoxysklerol® (Polidocanol) and Sotradecol® (Sodium Tetradecyl Sulfate) in the Management of Varixose Veins of the Lower Extremities

Study design: Randomized (Yes) Double Blind (Yes) Placebo controlled (No; active comparator: Sotradecol); Multicentered (No; single center)

Indication: from draft labeling (Vol. 30, p. 8): sclerotherapy of varicose veins of the lower extremities
Aethoxysklerol 0.5%: very small varicose veins (spider veins) ≤ 1 mm in diameter
Aethoxysklerol 1%: small varicose veins (b) (4) 1 to 3 mm in diameter

Study arms (dosage, duration, treatment length for each arm): from protocol (Vol. 31, p. 467):

Arms:
1. varicosities under 1mm in diameter: 0.5% Aethoxysklerol or 0.25% Sotradecol
2. varicosities over 1 mm up to 3 mm in diameter: 1.0% Aethoxysklerol or 0.5% Sotradecol
3. varicosities over 3 mm up to 6 mm in diameter: 3.0% Aethoxysklerol or 1.5% Sotradecol

*Note: Sotradecol was supplied by the sponsor in concentrations of 1.0% and 3.0% and diluted with parenteral solutions provided by the investigator (Vol. 31, p. 467).

Dosage:
"Each Study Center will determine the amount of sclerosing agent necessary to treat the affected area and the number of sclerotherapy sessions necessary to obtain results. The maximum dose of 2 mg/kg of Aethoxysklerol; 4 ml of Sotradecol 1.0% or 2 ml Sotradecol 3% per session will be strictly observed (Sec. 8.2.0 of protocol; Vol. 31, p. 471)."

Duration:
The duration of the trial varied for each subject according to the number of treatments received: "The final assessment of results will be made 4 months (16 weeks) after the last treatment received (Sec. 8.2.4 of protocol; Vol. 31, p. 473)."

Efficacy endpoints: Primary and secondary endpoints were not expressly identified in the original protocol. Section 10.0.0 of the protocol ("Criteria for Determining Efficacy"; Vol. 31, p.476) states, "The clinical response to treatment will be evaluated by the investigator by assessing the following endpoints":
a) photographic score (based on 3 factors: disappearance of varicosities, pigmentation and neovascularization)
b) overall patient satisfaction
c) assessment of subjective variables
d) incidence of systemic effects
e) discrete variables such as swelling and inflammation

Amendment #1 (cover letter dated July 6, 1995; Vol. 31, p. 510): changed the criteria for determining efficacy (changes found in Sec. 11.0.0 of the amended protocol, Vol. 31, p. 533):

- Primary endpoint: overall level of clinical improvement (definition unclear; Vol. 31. P. 534)
- Secondary endpoint: disappearance of varicosities

Amendment #2 [no cover letter but the facsimile date (e.g., top of p. 663) is January 29, 1997; the stamp date (?CDER) is also January 29, 1997; Vol. 31, p. 643)] further changed the endpoints (Section 11.0.0 of amended protocol, p. 663):

- Primary endpoint: disappearance of varicosities
- Secondary endpoint: overall clinical improvement

***Note**: Amendment #2 appears to have been submitted after both pivotal trials had been completed.

The clinical study reports (OHIO, Vol. 35, p. 2311; MICA Vol. 37, p. 3127) list the efficacy variables as:

- Primary: the disappearance of varicosities
- Secondary: 1) overall clinical improvement 2) overall patient satisfaction

How measured:

Disappearance of varicosities (as defined in Amendment #2 Vol. 31, p. 663; also see the study reports for the pivitol trials OHIO: Vol. 35, p. 2311 and MICA: Vol. 37, p. 3126):

This endpoint was to have been "independently judged and scored by three vascular surgeons who will provide their unbiased, objective grading based upon the comparison of a set of pre-injection baseline **photographs, with a set taken 16 weeks after the last treatment... To ensure a fair and reliable** photographic evaluation, the three independent reviewers will be instructed by the PI and study biostatistician in the assessment and scoring procedures in the course of a preparatory training session. The extent of disappearance of varicosities will be evaluated according to a 1-5 scale (where **5=compelete disappearance of varicosities)...**"

This definition was expanded in the clinical study reports for both clinical trials (Vol. 35, p. 2311; Vol. 37, p. 3127): "The average of the 'disappearance' scores from the 3 reviewers was used for the analyses of the primary efficacy variable. Based on this score, a categorical 'complete disappearance' variable was derived, where a value of 'yes' was given for **those cases which received a score of 5...and all** others were given a value of 'no.'" The sponsor submitted both analyses (i.e., disappearance scores and the dichotomized version of the disappearance assessment).

****

Pivotal Study #2: MICA (initiation: March 3, 1993; completion: February 19, 1996; Vol. 37, p. 3109)
Location: Protocol: Vol. 31, p. 453 **Study Report:** Vol. 35, p. 3109 (dated September 1, 1999)

Has the sponsor stated that this protocol is identical in design to Study #1? Implicitly: a single protocol was submitted as the "OHIO/MICA Protocol" (Vol. 31, p. 453).

Is this an adequate multi-centered trial? two centers; the data from the 2 centers were pooled; could not locate the number of subjects enrolled at each center

J. Leonel Villavicencio, M.D. (Prinicipal Investigator; Vol. 31, p. 747)
Uniformed Services University of the Health Sciences
Bethesda, MD

From Dermatology Associates of San Diego County, Inc. in Encinitas, CA (Vol. 31, p. 747):
1. (b) (4)
2. Mithcel P. Goldman, MD (Coordinating Investigator; Vol. 37, p. 3111)

From Institute for Vein Diseases in Southfield, MI (study report, Vol. 31, p. 747):
1. (b) (4)
2. John R. Pfeifer, MD (study report, Coordinating Investigator; Vol. 37, p. 3111)

174 enrolled and received study drug equally randomized to either Aethoxysklerol (72 subjects) or Sotradecol (77 subjects); 16 subjects were protocol violators, 9 subjects were did not complete the study; unclear how many subjects were enrolled per investigator and/or per site

Study Title: same

Study design: Randomized (Yes) **Double Blind** (Yes) **Placebo controlled** (No; active comparator: Sotradecol) **Multicentered** (Yes;/two centers)

Indication: same

Study arms (dosage, duration, treatment length for each arm): same

Efficacy endpoints (Primary and secondary): same

How measured: same

6. **Are the pivotal efficacy studies of appropriate design to meet basic requirements for approvability of this product based on proposed draft labeling?** No

Proposed indication from sponsor's draft labeling: from draft labeling (Vol. 30, p. 8): sclerotherapy of varicose veins of the lower extremities
Aethoxysklerol 0.5%: very small varicose veins (spider veins) ≤ 1 mm in diameter
Aethoxysklerol 1%: small varicose veins (b) 1 to 3 mm in diameter
(b) (4)

As designed, could endpoints in pivotal trial #1 support labeling? No

From Clinical Pharmacology Section of Draft Label:

(b) (4)

From Dosage and Administration Section of Draft Label:

(b) (4)

Comment: Pertaining to the Dosage and Administration" section, the protocol **did not** address

1. the specific volume(s) of product to administer per injection for any of the vessel sizes studied. (See Sec. 5.3.2 of protocol, Vol. 31, p. 464, "Route of Administration and Dosages Recommended;" Sec. 7.1.4, p. 467, "Study Design;" Sec. 8.2.0, p. 471, "Dosage and Administration"; Appendix 3, p. 503, "Treatment Guidelines Aethoxysklerol/Sotradecol Multicenter Trial."
2. positioning of patient during injection or application of compression
3. types of syringes or needles.
4. injection techniques
5. post-treatment ambulation
6. compression procedures or their impact on treatment success/treatment durability
7. Treatment intervals of 1 to 2 weeks

As designed, could endpoints in pivotal trial #2 support labeling? No; see response above

7. **Are all data sets for pivotal efficacy studies complete for all indications (indications) requested? (this is a stat question?)**

8. **Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?** No

PreIND Mtg: ?

IND number/s: 35,139

Guidance Meetings: January 12, 1998; September 23, 1998
EP2 Meeting Date: ?
Agency response to Phase 3 protocols: ?
PreNDA meeting date: October 21, 2002

Do endpoints as described by sponsor in pivotal Study 1 conform to previous agency commitments? No, not during the conduct of the trials (based on review of the protocol, Amendments 1 and 2 and their respective dates). Endpoints appear to have been amended post-hoc to conform with the primary endpoint recommended by the agency:

- February 8, 1994 Facsimile Memorandum to sponsor from FDA (Vol. 37, p. 3301): "... stated objective is to demonstrate...disappearance of varicosities...Pigmentation and neovascularization are...an adverse event...they should not be combined with your primary efficacy variable...we will evaluate efficacy separately form adverse events."
- October 4, 1996 FDA communication to sponsor (Vol. 37, p. 3531): "...disappearance of the vascularization...is the primary endpoint."
- January 12, 1998 Guidance Meeting: primary endpoint should be disappearance of vascularization as determined by three readers on a 5-point scale.
- September 23, 1998 Guidance Meeting: 1) primary endpoint should be disappearance of varicosities; FDA recommended that the sponsor consider the dichotomized version of disappearance of varicosities (yes/no) as the sole primary efficacy variable 2) minimum of 300 subjects treated with the labeled dosing and adequately followed for safety are required for filing; "to-be-marketed' formulation should have been used; referred to ICH E 1A.

Do endpoints as described by sponsor in pivotal Study 2 conform to previous agency commitments? As above

Are the pivotal trials multi-centered? OHIO was reported as single-center trial; MICA was reported as a two-center trial (sites in Michigan and California)

Are there adequate numbers of patients enrolled? No

9. **Has the applicant submitted line listings in a format to allow reasonable review of the patient data?** No

Has the applicant submitted line listings in the format agreed to previously by the Division? Not aware of any previous agreement

10. **Has the application submitted a rationale for assuming the applicability of foreign data (disease specific microbiologic specific) in the submission to the US population?** None found

11. **Has the applicant submitted all additional required case record forms (beyond deaths and drop-outs) previously requested by the Division?** Not aware of any previous requests

12. **Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously agreed to by the Division?** No; no table of

contents for the data listings. Integrated Summary of Safety is included in the submission.

13. **Has the applicant presented a safety assessment based on all current world-wide knowledge regarding this product?** Not specifically found; Foreign Marketing History is in Volume 2 (one sentence re product not having been withdrawn from marketing in any country (p.274). According to the Master Table of Contents, Safety Updates can be found in Volume 44; however, no update was found

14. **Has the applicant submitted draft -labeling consistent with 21CFR 201.56 and 21CFR 201.57, current divisional policies, and the design of the development package?** Draft labeling was submitted; not consistent with the design of the development package

15. **Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions with the Sponsor?** It is not clear that any special studies were requested.

16. **Has the applicant complied with the requirements of the Pediatric Rule?** waiver requested (Vol. 1)

    a) **Is this an indication that would be applicable to the pediatric population?** rare
    b) **What pediatric ages are included in the protocol?** none
    c) **Does the sponsor request pediatric labeling?** no
    d) **What waivers, if any, are requested?** Pediatric waiver requested ("studies impossible or highly impractical

17. **Financial disclosure of investigator**

    a) **Does the NDA contain the appropriate form to comply with the filing requirement for Financial Disclosure for Investigators?** Yes

18. **From a clinical perspective, is this NDA fileable? If "no", please state below why it is not.** No, for reasons which include:

    1. Presentation of the material in Section 8, "Clinical Data Section" is in so haphazard a manner as to render it incomplete on its face.
       a. There is no comprehensive table of contents for Volumes 35 through 43 (pages 2292A through 5427). Contents of these volumes include the individual Clinical Study Reports for the pivotal trials (MICA and OHIO) and the data listings.
       b. There is inadequate guidance in the study reports to the location of individual data and records.
    2. There is clear failure to include evidence of effectiveness compatible with the statute and regulations.
       a. There is a lack of adequate and well-controlled studies. The sponsor's comparator was Sotredecol, an approved sclerosant, which the sponsor supplied to investigators in the its manufactured concentrations of 1.0% and 3.0%. However, the protocol called for investigators to administer Sotradecol in the off-label concentrations of 0.25%, 0.5% and 1.5%. Even had this been acceptable, there were no instructions given as to the procedures

for dilution or for the solution to use as a diluent. Dilutions were achieved by use of parenteral solutions provided by the investigator.

b. The primary endpoint in the pivotal trials was inappropriate. The agency recommended that the primary endpoint be the disappearance of varicosities (see agency communciations/minutes from February 8, 1994, October 4, 1996, January 12, 1998, and September 23, 1998). The sponsor does not appear to have amended the protocol to reflect the recommended primary endpoint until after the pivotal trials were completed (see Amendment #2; submitted January 29, 1997). Further, the Principal Investigator and the study biostatistician instructed the three "independent" reviewers in the post-hoc scoring procedures, possibly introducing bias.

3. There is critical data, information or analyses needed to evaluate effectiveness and safety or provide adequate directions for use.
   a. The total patient exposure (numbers or duration) at relevant doses is clearly inadequate to evaluate safety. At the September 23, 1998 Guidance Meeting, the sponsor was advised that a minimum of 300 subjects treated with the labeled dosing and adequately followed would be required for safety, and the sponsor was referred to the ICH E1A document for additional discussion.
   b. There is clearly inadequate evaluation for effectiveness of the population intended to use the drug. The last study visit was 16 weeks (4 months) following the last treatment. This is not a sufficiently long to allow for the assessment of durability of treatment effect.
   c. There is an absence of data supporting the proposed dose and dose intervals. The pivotal trials did not study specific volume(s) of product to administer per injection for any of the vessel sizes studied. Also, the pivotal trials did not study dosing intervals of one to two weeks. Additionally, the pivotal trials did not assess
      i. positioning of patient during injection
      ii. types of syringes or needles.
      iii. injection techniques
      iv. post-treatment ambulation
      v. compression procedures or their impact on treatment success/treatment durability

If certain claims are not fileable please state which claims they are and why they are not fileable.

Brenda Carr, MD_____
Reviewing Medical Officer

_____
Medical Team Leader

Addendum: At the fileability meeting (November 24, 2003), it was concluded that the NDA would be fileable if the sponsor provided the comprehensive table of contents for Volumes 35 through 43 (pages 2292A through

5427). The sponsor was advised of the need for the comprehensive table of contents in a teleconference held on November 24, 2003 and that it should be submitted by November 28, 2003. The sponsor agreed to provide the requested information by this date.

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/s/

Brenda Carr
11/25/03 10:52:32 AM
MEDICAL OFFICER

Markham Luke
12/8/03 05:45:31 PM
MEDICAL OFFICER
Found to be fileable after Sponsor resolved TOC granularity issues. Efficacy and safety review issues outstanding to be communicated in 74-day letter. Not filing issues as per Fileability Meeting attended by DD and OD.

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # **21-201** Supplement # **N/A** SE1 SE2 SE3 SE4 SE5 SE6 SE7 SE8

Trade Name: **Aethoxysklerol**
Generic Name: **polidocanol**
Strengths: **0.5%, 1%,** (b) (4)

Applicant: **Chemische Fabrik Kreussler & Co., GmbH**

Date of Application: **September 29, 2003**
Date of Receipt: **October 2, 2003**
Date clock started after UN:
Date of Filing Meeting: **November 10, 2003**
Filing Date: **December 15, 2003**
Action Goal Date (optional): User Fee Goal Date:

Indication(s) requested: Treatment of varicose veins of the lower extremities.

Type of Original NDA: (b)(1) __**X**_____ (b)(2) _____
OR
Type of Supplement: (b)(1) _____ (b)(2) _____

NOTE: A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2) application, complete the (b)(2) section at the end of this review.

Therapeutic Classification: S ___**X**_____ P _____
Resubmission after withdrawal? ___**YES**___ Resubmission after refuse to file? _____
Chemical Classification: (1,2,3 etc.) ___**1**_____
Other (orphan, OTC, etc.) _____

User Fee Status: Paid _____ Exempt (orphan, government) _____
Waived (e.g., small business, public health) _**X**_____

Form 3397 (User Fee Cover Sheet) submitted: **X** YES NO

User Fee ID # _____
Clinical data? YES __**X**_____ NO, Referenced to NDA # _____

Is there any 5-year or 3-year exclusivity on this active moiety in either a (b)(1) or a (b)(2) application?

YES **X** NO

If yes, explain:

Does another drug have orphan drug exclusivity for the same indication? YES **X** NO

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?

X N/A YES NO

Is the application affected by the Application Integrity Policy (AIP)? YES **X** NO
If yes, explain.

If yes, has OC/DMPQ been notified of the submission? **X N/A** YES NO

- Does the submission contain an accurate comprehensive index? **X** YES NO
- Was form 356h included with an authorized signature? **X** YES NO
  If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? **X** YES NO
  If no, explain:
- If an electronic NDA, does it follow the Guidance? **X** N/A YES NO
  If an electronic NDA, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?

  Additional comments:
- If in Common Technical Document format, does it follow the guidance? **X** N/A YES NO
- Is it an electronic CTD? **X** N/A YES NO
  If an electronic CTD, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?

  Additional comments:
- Patent information submitted on form FDA 3542a? **X** YES NO
- Exclusivity requested? YES, _____years **X** NO
  Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.
- Correctly worded Debarment Certification included with authorized signature? **X** YES NO
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., *"[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application."* Applicant may not use wording such as "To the best of my knowledge . . . ."

- Financial Disclosure forms included with authorized signature? **X** YES NO
  (Forms 3454 and 3455 must be used and must be signed by the APPLICANT.)

- Field Copy Certification (that it is a true copy of the CMC technical section)? **X** YES NO

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? **X** YES NO
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.

- List referenced IND numbers: 35,139

- End-of-Phase 2 Meeting(s)? Date(s) _____ NO
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) October 21, 2002 NO
  If yes, distribute minutes before filing meeting.

Project Management

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?
  *Note: Will send consult after application is filed. YES **X** NO

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? YES **X** NO
  *Note: Will send consult after application is filed.

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A YES **X** NO
  *Note: Will send consult after application is filed.

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?
  X N/A YES NO

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS?
  X N/A YES NO

- Has DOTCDP been notified of the OTC switch application? **X** N/A YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
  X N/A YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? **X** YES NO
  If no, did applicant submit a complete environmental assessment? **X** N/A YES NO
  If EA submitted, consulted to Nancy Sager (HFD-357)? **X** N/A YES NO

- Establishment Evaluation Request (EER) submitted to DMPQ? **X** YES NO

- If a parenteral product, consulted to Microbiology Team (HFD-805)? **X** YES NO

If 505(b)(2) application, complete the following section:

- Name of listed drug(s) and NDA/ANDA #:

- Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

- Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs.)
  YES NO

- Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 314.101(d)(9).
  YES NO

- Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD? (See 314.54(b)(2)). If yes, the application should be refused for filing under 314.101(d)(9).
  YES NO

- Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

  ____ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

  ____ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

  ____ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

  ____ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].

____ 21 CFR 314.50(i)(1)(ii): No relevant patents.

____ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications.

____ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above.)
____ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

- Did the applicant:
  - Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?

    YES NO
  - Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

    YES NO
  - Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

    N/A YES NO
  - Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?

    N/A YES NO
- If the (b)(2) applicant is requesting exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):
  - Certification that each of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

    YES NO
  - A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

    YES NO
  - EITHER
    The number of the applicant's IND under which the studies essential to approval were conducted.

IND # _____ NO

OR

A certification that it provided substantial support of the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

N/A YES NO

- Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?

YES NO

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/s/

Leonthena Carrington
12/16/03 10:45:58 AM
CSO
NDA 21-201 Regulatory Filing Review

Mary Jean Kozma Fornaro
12/16/03 11:04:21 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING REVIEW LETTER

NDA 21-201

Chemische Fabrik Kreussler & Co., GmbH
c/o INC Research, Inc.
Attention: Howard M. Smith
675 Peter Jefferson Parkway
Suite 120
Charlottesville, VA 22911

Dear Mr. Smith:

Please refer to your September 29, 2003, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Aethoxysklerol (polidocanol) Injectable, 0.5%, 1%, (b) (4)

We have completed our filing review, and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on December 1, 2003, in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

Clinical:

1) The total patient exposure (numbers or duration) at relevant doses is insufficient to adequately evaluate safety at the doses proposed. At the September 23, 1998, Guidance Meeting, you were advised that a minimum of 300 subjects treated with the labeled dosing and adequately followed would be required for safety, and you were referred to the ICH E1A document for additional discussion.

2) Specific and detailed instructions to allow for safe and effective use of the drug product have not been provided. This information should be supported with sufficient data to conclude that such use allows for safe and effective use. For example, the pivotal trials did not assess:
   a) positioning of patient during injection
   b) types of syringes or needles
   c) injection techniques
   d) post-treatment ambulation
   e) compression procedures or their impact on treatment success/treatment durability

3) There is an absence of data supporting the proposed dose and dose intervals in the provided draft labeling. The pivotal trials did not study specific volume(s) of product to

administer per injection for any of the vessel sizes studied. Also, the pivotal trials did not study dosing intervals of one to two weeks.

4) There is inadequate evaluation for effectiveness in the intended population for the proposed indication. The last study visit was 16 weeks (4 months) following the last treatment. This is not sufficient to allow for the assessment of durability of treatment effect, which is a key component of the efficacy of this therapy. Disappearance of varicosities is acceptable as an efficacy variable; however, an efficacy endpoint at 16 weeks after the last treatment is not of sufficient duration to allow determination of the durability of the treatment effect.

5) Two studies are identified as pivotal, one single center OHIO Study and one 2-center MICA Study. While data from these studies may be sufficient to support filing of the application, the submitted data appear insufficient to make a determination of efficacy to support product approval.

6) Sotradecol was used at a lower concentration than the currently approved drug product. The diluted Sotradecol should therefore be considered a placebo for the purposes of study and a determination should be made of superiority of Aethoxysklerol over the diluted Sotradecol.

Biostatistics:

1) Photographs are said to be graded by three independent reviewers. It is not clear if all photographs in a study are graded by the same reviewers or not.

2) At each center, several co-investigators are listed. It is not clear if these investigators treat different subsets of patients or not, or if all patients are treated by the same investigators.

3) Your facsimile, dated January 29, 1997, states that the primary efficacy endpoint will be the disappearance of varicosities, with clinical improvement as a secondary endpoint. These are to be tested for superiority over the comparator drug. However, your own analyses, as reported in the integrated summary of efficacy, do not show statistically significant treatment differences.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon or modified as we review the application.

We also request that you submit the following information to address the potential review issues described above:

Biopharmaceutics:

1) It appears that only Japanese patients were enrolled in the pivotal PK study (ASK-00-01-00). Please provide systemic exposure information of Aethoxysklerol in patients that would represent the U.S. population (e.g., Caucasian, African-American, Hispanic, etc.).

Clinical:

1) Please clarify how the efficacy evaluation was carried out by the three investigator review.
2) Does each of the three investigators rate the same photograph or do different investigators rate different photographs? If the three investigators rated the same photograph, please clarify how the overall subject/patient rating was carried out.
3) Please clarify whether a different panel of investigators rated subjects in the different studies or the same investigators rated the subjects in the two studies.
4) Please provide correlation of the relevance for the photographic evidence versus the actual clinical assessment of the patients. Further, how does the photographic evidence relate to the longevity of effect?
5) Please submit baseline and efficacy endpoint assessment photographs for each and every patient with complete disappearance of varicosities.
6) Please provide photographs that would enable the Agency to evaluate the grading scale.
7) Please provide the location in the NDA of the names of the photographic review panel and CVs and financial disclosure for each reviewer.
8) Please provide information regarding bioavailability in the pulmonary circulation after venous injection of Aethoxysklerol. Please comment on potential for longer term side effects with pulmonary exposure, e.g., pulmonary hypertension.

Biostatistics:

1) Please provide whether different sets of reviewers are used for photograph grading, both within and between studies.
2) Please clarify if co-investigators at each center treat all patients or different subsets of patients.

Please respond to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Lea Carrington, Regulatory Project Manager, at (301) 827-2020.

Sincerely,

{See appended electronic signature page}

Jonathan Wilkin, M.D.
Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jonathan Wilkin
12/15/03 11:41:00 AM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V

FACSIMILE TRANSMITTAL SHEET

DATE: November 26, 2003

To: Howard M. Smith, Senior Director Regulatory Operations & Medical Writing	**From:** Lea Carrington Regulatory Project Manager
Company: Chemische Fabrik Kruessler & Co. c/o INC Research	Division of Dermatologic & Dental Drug Products
Fax number: (434) 295-7209	**Fax number:** (301) 827-2091 or 2075
Phone number: (434) 244-5165	**Phone number:** (301) 827-2020

Subject: **NDA 21-201**

Total no. of pages including cover: 2

Comments: **Biopharmaceutics comments – to expedite, please fax by Dec. 1, 2003.**

Document to be mailed: • YES ☑ NO

FDA Fax Memorandum

Date: November 26, 2003

To: Howard M. Smith, Senior Director
Regulatory Operations & Medical Writing

Applicant: Chemische Fabrik Kruessler & Co.
c/o INC Research

Subject: NDA 21-201 Information Request

Dear Howard,

The Biopharm reviewer has requested additional information regarding your submission of New Drug Application (NDA) 21-201, Aethoxysklerol (polidocanol) 0.5%, 1%,(b) (4) (b) (4). Please fax the requested information by December 1, 2003, and in addition please provide your response as an official submission to your NDA.

Biopharm Comments:

1. Please provide the source and identification information of the drug substance and the dosage form used in the pivotal PK study ASK-00-01-00; and confirm whether they are the same as the to-be-marketed drug substance and dosage form.

2. Please submit the clinical study report for ASK-00-01-00 in an electronic format if available.

Please contact me should you have any questions.

Respectfully,

Lea Carrington
Regulatory Project Manager

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/s/

Leonthena Carrington
11/26/03 12:53:18 PM
CSO

Biopharm comments faxed 11/26/03.

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V

FACSIMILE TRANSMITTAL SHEET

DATE: November 26, 2003

To: Howard M. Smith, Senior Director Regulatory Operations & Medical Writing	**From:** Lea Carrington Regulatory Project Manager
Company: Chemische Fabrik Kreussler & Co. c/o INC Research	Division of Dermatologic & Dental Drug Products
Fax number: (434) 295-7209	**Fax number:** (301) 827-2091 or 2075
Phone number: (434) 244-5165	**Phone number:** (301) 827-2020

Subject: **NDA 21-201: Information request**

Total no. of pages including cover: 3

Comments: Specific detail for Table of Contents requested; please fax by Dec. 1, 2003.

Document to be mailed: • •YES ☑ NO

FDA Fax Memorandum

Date: November 26, 2003

To: Howard M. Smith, Senior Director
Regulatory Operations & Medical Writing

Applicant: Chemische Fabrik Kreussler & Co.
c/o INC Research

Subject: NDA 21-201 Information Request

Dear Howard,

The Medical Officer has requested additional information to facilitate review of your submission of New Drug Application (NDA) 21-201, Aethoxysklerol (polidocanol) 0.5%, 1%, (b) (4) Please fax the requested information by December 1, 2003, and in addition please provide your response as an official submission to your NDA.

Clinical Comments:

Please provide additional detail in the Table of Contents (TOC) for the clinical lab data in Volume 1, beginning on page 4948. All the data are listed as **"Clinical Laboratory Results" and do not identify what type of lab** might be found on a particular page. For example, the TOC does not identify the specific page location of hematologic analyses or urinalyses.

This specific information will prevent the reviewer from randomly searching through all the lab data to find a specific data listing.

Please contact me should you have any questions.

Respectfully,

Lea Carrington
Regulatory Project Manager

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/s/

Leonthena Carrington
11/26/03 04:01:29 PM
CSO
Clinical information request faxed to sponsor 11/26/03.

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V

FACSIMILE TRANSMITTAL SHEET

DATE: November 10, 2003

To: Howard M. Smith, Senior Director Regulatory Operations & Medical Writing	**From:** Lea Carrington Regulatory Project Manager
Company: Chemische Fabrik Kruessler & Co. c/o INC Research	Division of Dermatologic & Dental Drug Products
Fax number: (434) 295-7209	**Fax number:** (301) 827-2091 or 2075
Phone number: (434) 244-5165	**Phone number:** (301) 827-2020

Subject: **NDA 21-201**

Total no. of pages including cover: 4 & copy of Form FDA 3542a (4 pages).

Comments: **Information Request – please provide by Nov. 21, 2003.**

Document to be mailed: • •**YES** ☑ **NO**

FDA Fax Memorandum

Date: November 10, 2003

To: Howard M. Smith, Senior Director
Regulatory Operations & Medical Writing

Applicant: Chemische Fabrik Kruessler & Co.
c/o INC Research

Subject: NDA 21-201 Information Request

We refer to your submission of New Drug Application (NDA) 21-201, Aethoxysklerol (polidocanol) 0.5%, 1%, (b) (4) **Please provide the documentation listed below in an official submission to your NDA by November 21, 2003 or please advise when the requested information will be submitted:**

Project Management

1. Form FDA 356h signed by the Applicant.

2. Debarment Certification signed by both the Applicant and the U.S. Agent in the format of the Draft Guidance for Industry - ***Submitting Debarment Certification Statements Draft Guidance*** which states:

   The FDA regards the following wording, taken from section 306(k)(1) of the Food, Drug and Cosmetic Act, as the most acceptable form of certification:

   [Name of the applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

3. Financial Disclosure Form 3454 signed by the Applicant.

4. Field Copy Certification signed by the Applicant.

5. Patent Information Form FDA 3542a signed by Applicant and U.S. Agent. (see attached)

Pharm/Tox

1. Please propose appropriate limits for all degradation products and supply data and reasoning for supporting the proposed limits.

2. The tabular data that comprises references 47, 48, 51, 52, & 56 should be linked to their associated GLP study reports. It appears that these tables may be associated with a study report included as reference #46. If these tables are not associated with reference #46, then the study reports associated with these tables should be submitted to the NDA.

Chemistry, Manufacturing and Controls

1. Please provide two additional copies of the methods validation package (volumes 15-17). Because they are not subject to our validation, the following may be omitted from these copies for compactness, and should be replaced with a single page indicating the page number range of the omitted pages:
    a. all specifications and analytical methods for materials used in the synthesis of polidocanol;
    b. all validation reports for these methods;
    c. all specifications and analytical methods for raw materials used in the manufacturing of all strengths of the finished drug product; and
    d. all in-process test procedures.

2. Please propose an appropriate limit for [redacted] (b) (4) in the drug product. This should be supported by data and your reasoning for the proposed limit. Based on comments from our pharmacologists, some persons have hypersensitivity to [redacted] (b) (4).

3. Please provide an estimate of the date on which you will be able to submit the 9- and 12-month stability updates for the lots of the drug product manufactured at [redacted] (b) (4) r [redacted] (b) (4)

4. Please clarify whether the primary stability batches are only those manufactured by [redacted] (b) (4), or if they include those manufactured by [redacted] (b) (4).

5. If the batches manufactured by [redacted] (b) (4) are to be considered as primary stability batches for our review, please verify that this facility is ready for inspection.

6. Please submit a report of the validation of the ampoule sealing (container and closure system integrity).

7. Please submit a validation summary of the bioburden reduction process (*i.e.*, the [redacted](b) (4)). A description of media fill methods and data summaries would adequately address this.

8. The drug substance testing facility identified as [redacted](b) (4) appears to also be known as [redacted](b) (4), which is located at the exact same address. Are they the same?

Please contact me if you have any additional questions.

Respectfully,

Lea Carrington
Regulatory Project Manager

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/s/

Leonthena Carrington
11/10/03 04:27:47 PM
CSO
Faxed to Applicant 11/10/2003.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-201

Chemische Fabrik Kreussler & Co.
c/o INC Research
Attention: Howard M. Smith
Senior Director, Regulatory Operations & Medical Writing
675 Peter Jefferson Parkway
Suite 120
Charlottesville, VA 22911

Dear Mr. Smith:

We have received your new drug application (NDA) submitted on behalf of Chemische Fabrik Kreussler & Co., under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Polidocanol (aethoxysklerol) Injectable

Review Priority Classification: Standard (S)

Date of Application: September 29, 2003

Date of Receipt: October 2, 2003

Our Reference Number: NDA 21-201

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on December 1, 2003, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be August 2, 2004.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Dermatologic & Dental Drug Products, HFD-540
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic & Dental Drug Products, HFD-540
9201 Corporate Boulevard
Rockville, Maryland 20850

If you have any questions, call Lea Carrington, Regulatory Project Manager, at (301) 827-2020.

Sincerely,

{See appended electronic signature page}

MARY JEAN KOZMA-FORNARO
SUPERVISOR, PROJECT MANAGEMENT
Division of Dermatologic & Dental Drugs
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/s/

Leonthena Carrington
11/4/03 03:36:01 PM
Signed for MJ Kozma-Fornaro.

inc
Research

Howard M. Smith certifies for Chemische Fabrik Kreussler & Co., GmbH that the field copy is a true copy of the application described in 21 CFR 314.50 (l)(3) and contained in the archival and review copies of the application.

Signature: Howard Smith

Date: 29 SEP 2003

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004.

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

Chemische Fabrik Kreussler & Co., GmbH
Rheingaustrasse 87-93
D-65203 Wiesbaden
Germany

2. TELEPHONE NUMBER *(Include Area Code)*

(434) 244-5165 (INC Research)

3. PRODUCT NAME

Aethoxysklerol

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

21-201

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

☒ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

_____
(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER

Request 99.045

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7, reverse side before checking box.)

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY
(Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☒ YES ☐ NO

(See item 8, reverse side if answered YES)

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Ann Smith	Senior. Director, Regulatory Operations & Medical Writing	29 SEP 2003

Department of Health and Human Services Public Health Service

Food and Drug Administration
Rockville, MD 20857

SEP 28 1999

Ellen C. Teplitzky, Esq.
Director, Contracts and Legal Affairs
PRA International
4105 Lewis & Clark Drive
Charlottesville, VA 22911-5801

RE: Chemische Fabrik Kreussler & Co., Aethoxysklerol (polidocanol)
Small Business Waiver Request 99.045

Dear Ms. Teplitzky:

This letter responds to your April 6 and May 28, 1999, letters to the Office of the Chief Mediator and Ombudsman, Food and Drug Administration (FDA), requesting a waiver of the prescription drug application fee for Aethoxysklerol (polidocanol) on behalf of Chemische Fabrik Kreussler & Co. (Kreussler) under the small business waiver provision of section 736(d)(1)(E) of the Prescription Drug User Fee Act of 1992 (PDUFA) as amended by the Food and Drug Administration Modernization Act of 1997 (Modernization Act) (Waiver Request 99.045). We apologize for the delayed response. Responsibilities related to certain waivers were transferred recently from the Chief Mediator and Ombudsman to the Associate Director for Policy at the Center for Drug Evaluation and Research. For the reasons described below, the FDA grants the request from Kreussler for a small business waiver.

According to your request for a waiver of fees, Kreussler is a small business operating in Wiesbaden, Germany, with fewer than 500 employees, including employees of affiliates. You state that the new drug application (NDA) to be submitted for Aethoxysklerol will be the first human drug application Kreussler submits to the Secretary for review. You also state that Aethoxysklerol is a sclerosing agent used for the treatment of varicose veins.

Under PDUFA as amended, a waiver of the application fee shall be granted to a small business for the first human drug application that a small business or its affiliate[1] submits to the FDA for review. The small business waiver provision entitles a qualified small business to a waiver when the business meets two criteria: first, a business must employ fewer than 500 persons, including employees of its affiliates; and second, the marketing application must be the first human drug application, within the meaning of PDUFA, that a company or its affiliate submits to FDA.

[1] "The term 'affiliate' means a business entity that has a relationship with a second business entity if, directly or indirectly – (A) one business entity controls, or has the power to control, the other business entity; or (B) a third party controls, or has power to control, both of the business entities" (21 U.S.C. 379g(9)).

FDA's decision to grant a small business waiver to Kreussler is based on two findings. First, by letter dated July 9, 1999, the Small Business Administration (SBA) determined that, as of June 15, 1999, Kreussler had fewer than 500 employees, including employees of its affiliates. According to the SBA, Kreussler's affiliates include: Ceteform Chemisch-Technische Fabrikation organischer Reinigungsmittel GmbH, Kreussler & Co. Produits Chimiques S.A.R.L., Kreussler & Co. Ltd., Kreussler Verwaltungs KG, Jablonski GmbH, and J. Simon & Duerkheim Chemische Fabrik GmbH. Second, according to FDA records, the marketing application for Aethoxysklerol is the first human drug application, within the meaning of PDUFA, to be submitted to FDA by Kreussler or its affiliates.

Consequently, your request for a small business waiver of the application fee for Aethoxysklerol is granted, provided that FDA receives the marketing application no later than December 15, 1999, six months after the effective date of the size determination made by SBA. Please note that once the marketing application is submitted, if FDA refuses to file the marketing application, or if Kreussler withdraws the marketing application before it is filed by FDA, a reevaluation of the waiver may be required should the company resubmit its marketing application. If this situation occurs, Kreussler should contact this office, approximately 90 days before it expects to resubmit its marketing application, about whether Kreussler continues to qualify for a small business waiver.

Please include a copy of this letter in the marketing application for Aethoxysklerol. If any billing questions arise concerning the marketing application, please contact Beverly Friedman or Michael Jones at 301-594-2041.

FDA plans to disclose to the public information about its actions granting or denying waivers and reductions. This disclosure will be consistent with the laws and regulations governing the disclosure of confidential commercial or financial information.

If you have any questions about this small business waiver, please contact Kathleen Locke at 301-594-2041.

Sincerely,

Jane A. Axelrad

Jane A. Axelrad
Associate Director for Policy
Center for Drug Evaluation and Research