CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-043

CORRESPONDENCE

HFD-560 Benson

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

OCT 2 1998

Soltec Research
Attention: Thomas Blake, R.Ph.
Regulatory Consultant
48 Mt. Olive Road
Budd Lake, New Jersey 07828

OCT - 8 1998

Dear Mr. Blake:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for Rid Mousse (pyrethrins 0.33%, piperonyl butoxide 4.0%) aerosolized mousse.

You were notified in our letter dated September 8, 1998 that your application for Rid Mousse (pyrethrins 0.33%, piperonyl butoxide 4.0%) aerosolized mousse was not accepted for filing due to non-payment of fees.

This is to notify you that the Agency has received all fees owed and your application has been accepted as of September 9, 1998.

The review priority classification for this application is Standard (S).

Unless we notify you within 60 days of the above date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on November 8, 1998 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be November 9, 1999.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

If you have any questions, contact Babette Merritt, Project Manager at (301) 827-2222.

Sincerely,

/S/

Maria Rossana R. Cook, M.B.A.
Supervisor, Project Management Staff
Division of Over-the-Counter Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Rockville MD 20857

NDA 21-043

JAN 11 1999

Soltec Research USA
Attention: Attention: Thomas Blake, R.Ph.
Regulatory Consultant to Soltec
48 Mt. Olive Road
Budd Lake, NJ 07828

Dear Mr. Blake:

Please refer to your pending August 31, 1998 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rid Mousse (pyrethrum extract, 0.33% and piperonyl butoxide, 4% aerosolized mousse).

We are reviewing your submission and have identified the following comments and information requests with regard to the chemistry, manufacturing, and controls, clinical, and summary sections of your NDA:

1. The incorrect CFR citation was provided in the Summary section for the claim of categorical exclusion for environmental assessment. Please submit a statement as provided for in 25.15(d) in the current 21 CFR if you qualify under part 25.31(b).

2. Letter of Authorization for Drug Master File (DMF) should be sent to the respective DMF, not to the reviewing division. The correct address is:

   Food and Drug Administration
   Center for Drug Evaluation and Research
   Central Document Room
   12229 Wilkins Avenue
   Rockville, Maryland 20852

3. We have no record of any DMFs submitted by [redacted] however, it has been determined that the information to be referenced to these DMFs is not essential to our review of the CMC section of this NDA.

4. Please provide quantitative data on how fast the foam collapses after being dispensed.

5. Please provide data on the concentrations of the piperonyl butoxide and pyrethrum extract in the product at the time when it is actually applied.

6. Please provide data on what percentage of the propellant flashes off and how much remains dissolved in the product.

7. Since you have formulated your product at the maximum concentrations allowable under the monograph, the assay limits will have to be 90.0 to 100.0% of the labeled amount for each active component. Consequently, a release assay value over 100.0% for either active will result in rejection of that batch since the higher amount is outside the limits set in the monograph.

8. Case report forms for adverse events need to be submitted for the aerosol formulation from previous marketing.

9. A statement that all nonclincal laboratory studies were conducted in compliance with the requirements set forth in Part 58 or a statement why a study was not conducted in compliance with those requirements should be submitted.

10. The debarment certification should be submitted.

11. Copies of all package inserts (or their equivalent) from all countries in which this product has been previously approved for marketing should be submitted. English translations should be provided for all non-English package inserts.

12. We note that your proposed labeling contains in capital letters, "USE ON DRY HAIR" and the mousse formulation contains approximately [redacted] water. Please explain the justification for the high water content in light of that direction.

We would appreciate your prompt written response so that we can continue our evaluation of your NDA.

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may

identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

If you have any questions, please contact Babette Merritt, Project Manager, at (301)-827-2222.

Sincerely yours,

/S/

Maria Rossana R. Cook, M.B.A.
Supervisor, Project Management Staff
Division of Over-the-Counter Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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Soltec RESEARCH
ACN 006 362 93
3 MACRO COURT
ROWVILLE, VICTORIA
AUSTRALIA 3178
TEL + 61 3 9753 0022
FAX + 61 3 9753 0354

ORIG AMENDMENT
BZ

February 19, 1999

Maria Rossana R. Cook
Division of Over-the-Counter Drug
Products (HFD-560)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, Maryland 20850

Subject: dNDA 21-043 for RID Mousse

Dear Ms. Cook:

This responds to your Information Request (IR) Letter dated 11 January 1999, the official copy of which we received on 21 January, and to your (and Ms. Babette Merritt's) additional requests during our telephone conversation of 11 February 1999. For ease of review, we have formatted this response to correspond to the sequence in your letter and during the T-con.

At the outset, please refer to our application as an NDA deviation, or dNDA, not an NDA since there are several issues yet to be resolved regarding the requirements for this new breed of submission. For example, can we assume that the flexibility of labeling regulation [21 CFR 330.1(c)(2)(ii) & (iii)] applies to the RID Mousse, an OTC monograph product in all respects but its dosage form; should annual reporting, if required at all, be limited only to the CMC portion; will ADE reporting be required, and if so, to what extent? Etc., etc., etc. The last substantive paragraph on page 3 of the cover letter to our dNDA requests the agency to consider these issues, especially since your declarations will be precedent-setting.

Following, then, are our responses to your specific requests in the prescribed order:

SOLTEC RESEARCH USA
[illegible] AVENUE SUITE 9 FALLS CHURCH, VA 22046 USA TEL (703) 533 [illegible] FAX (703) 532 0557
E-mail deerrt@FC DEFGRP COM

1. The incorrect CFR citation was provided in the Summary section for the claim of categorical exclusion for environmental assessment. Please submit a statement as provided for in 25.15(d) in the current 21 CFR if you qualify under part 25.31(b).

   Incorporating administrative changes in the environmental impact regulations, the revised statement in the Summary section now reads:

   "Under the provisions of 25.15(d) and 25.31(b), we are requesting a categorical exclusion from the requirements to submit on Environmental Assessment."

   The Environmental Assessment portion of the dNDA (page 649) was altered accordingly. It now reads:

   ENVIRONMENTAL ASSESSMENT

   A claim for categorical exclusion is made under 21 CFR 25.15(d) and 25.31(b), the environmental regulations which exempts monographed OTC drugs. The active ingredients in the pediculicide mousse, pyrethrins and piperonyl butoxide, are marketed widely in a host of nonprescription products. Further, the propellant consists of natural hydrocarbons -- propane, isobutane, n-butane -- which appear on EPA's list of Acceptable Substitutes for Aerosol Propellants which were published as part of its Significant New Alternatives Policy (first page immediately appended). It, too, is commonly used in foam-type OTC preparations. Consequently, introduction of the mousse product is expected to have no measurable incremental effect upon the environment.

   Thank you for acquainting us with the recodified environmental impact regulations.

2. Letter of Authorization for Drug Master File (DMF) should be sent to the respective DMF, not to the reviewing division. The correct address is:

   Food and Drug Administration
   Center for Drug Evaluation and Research
   Central Document Room
   12229 Wilkins Avenue
   Rockville, Maryland 20852

The deed is done. Please note that [redacted] the ultimate manufacturer of RID Mousse, did send a copy of its DMF to the Central Document Room before the dNDA was filed.

3. We have no record of any DMFs submitted by [redacted] however, it has been determined that the information to be referenced to these DMFs is not essential to our review of the CMC section of this NDA.

Primarily a broker, [redacted] receives its pyrethrum extract and piperonyl butoxide from outside sources. By this time, the Central Document Room should have received Letters of Authorization from the [redacted] supplier of the piperonyl butoxide, for the two active ingredients in RID Mousse. We will send you the DMF numbers when we receive them.

4. Please provide quantitative data on how fast the foam collapses after being dispensed.

In response to your request, an *in vitro* experiment was conducted to determine how long the actuated RID Mousse [redacted] when left undisturbed. Three cans each were tested from three different lots. [redacted]

Of course this is an unnatural situation since, much as with the commercial OTC pyrethrin/piperonyl butoxide shampoos, consumers are directed in product labeling to massage the mousse well into the hair. RID Mousse carries additional directions for people with long hair. Consequently, an additional experiment was conducted to simulate this mechanical action [redacted]

The two experiments constitute Attachment 1.

5. Please provide data on the concentrations of the piperonyl butoxide and pyrethrum extract in the product at the time when it is actually applied.

Your inquiry prompted an *in vitro* simulation of the human act of applying, that is massaging the mousse into the hair, [redacted]

(labeling calls for the product to remain in the hair for 10 minutes before being washed off). Cans from three lots were tested. of the OTC monograph's maximum allowable strength. In no instance did any single value fall outside this range.

Finally, it should be pointed out that like other pediculicides, while concentrations of drug may change from container to hair, the total dosage remains the same.

This application/concentration experiment may be found in Attachment 2.

6. Please provide data on what percentage of the propellant flashes off and how much remains dissolved in the product.

An experiment similar to the one described above, where actual use conditions were simulated and measurements made, showed that the percentage of propellant flash-off varied from after one minute, and from after ten minutes in product from the three lots tested.

Conversely, the percentage of propellant remaining dissolved in the product ranged from after one minute, and from after ten minutes.

Results of this application/propellant experiment are contained in Attachment 3.

7. Since you have formulated your product at the maximum concentrations allowable under the monograph, the assay limits will have to be of the labeled amount for each active component. Consequently, a release assay value over 100.0% for either active will result in rejection of the batch since the higher amount is outside the limits set in the monograph.

Following this admonition would cause RID Mousse to be adulterated and misbranded. We are aware of no drug specification, USP or otherwise where the upper potency limit is exactly 100% of label claim. Invariably, ranges are given, e.g. ±10%, either due to the nature of the drug and its manufacturing processes, or because the analytical techniques themselves demand certain

tolerances. With an analytical specification of [ ] for its packaged lot release, RID Mousse would need to be formulated at [ ] of target concentration in order to insure that no active ingredient could exceed the limits set by the OTC monograph. This would put the drug in direct violation of 21 CFR 211.101(a) which requires manufacturers to formulate to 100% of label claim.

Like every other drug of which we are aware, RID Mousse must be manufactured to 100% of label claim to meet this GMP regulation. This requires certain tolerances, i.e. ±10% of label claim, to be accepted.

8. Case report forms for adverse events need to be submitted for the aerosol formulation from previous marketing.

As you know, case report forms are not used for FDA's Spontaneous Reporting System, or Medwatch, for tracking Adverse Drug Experiences with marketed products, but the Form FDA 3500 format is.

Even though the formulations are different and the Adverse Experiences are for BanLice, sold only in Australia, we nonetheless converted the reports to the U.S. system. These may be found in Attachment 4.

Following are summary tables for both the U.S. vs. Australian formulations and the ADEs reported for BanLice, the Australian product:

PEDICULICDE MOUSSE: U.S. VS. AUSTRALIAN FORMULAS

	BanLice (Australia)	*RID Mousse (U.S.)*
pyrethrins	0.168%	0.33%
piperonyl butoxide	1.68%	4%

RANLICE* - AUSTRALIAN ADVERSE EVENTS

Index #	*Sex*	*Age*	*Event*	*To Pfizer*
9615439	F	8	Lightening/bleaching of hair	26/04/94
9615440	F	unk	Lightening/bleaching of hair	26/04/94
9615441	F	11	Rash/allergic reaction	16/06/94
9706411	F	unk	Hair damages	17/03/97
9707428	F	unk	Allergic skin reaction	01/04/97
9710741	F	unk	Itchy, irritated scalp	12/05/97
9713009	F	unk	Headache, nausea	12/06/97
9715814	F	55	Allergic reaction - rash	21/07/97
9803061	F	unk	Burning L hand	30/01/98
9803062	F	5	Burning on scalp	30/01/98
9813130	F	6	Bald spot	20/04/98
9824634	F	unk	Numbness, nausea	04/08/98

*0.168% pyrethrins
1.68% piperonyl butoxide

9. A statement that all nonclinical laboratory studies were conduced in compliance with the requirements set forth in Part 58 or a statement why a study was not conducted in compliance with those requirements should be submitted.

The nonclinical laboratory studies submitted in this supplement, i.e. Ovicidal Activity (Study No. 016-0049) and Adulticidal Activity (Study No. 016-0048) were conducted as a demonstration of product effectiveness. Further, the studies were not conducted for purposes of determining safety and therefore do not meet the definition of "nonclinical laboratory study" as defined by 21 CFR 58.3(d). Requirements of Part 58, as a whole, do not apply to these studies.

That said, the studies were conducted by [redacted] laboratory which routinely performs insecticide studies. The firm is EPA-inspected.

10. The debarment certification should be submitted.

The debarment certification may be found on page 709 of the dNDA.

11. Copies of all package inserts (or their equivalent) from all countries in which this product has been previously approved for marketing should be submitted. English translations should be provided for all non-English package inserts.

RID Mousse, with its maximum strength OTC monograph ingredients, is sold nowhere in the world.

However, we are providing labeling for BariLice, a product with a slightly different formula (see Item 8), which is sold only in Australia. Attachment 5 contains the Australian labeling.

12. We note that your proposed labeling contains in capital letters, "USE ON DRY HAIR" and the mousse formulation contains approximately [redacted] water. Please explain the justification for the high water content in light of that direction.

The [redacted] water content is necessary for formulation purposes and is little different than that used in other commercial preparations marketed under the OTC monograph. In response to your inquiry, we are analyzing the water content of two competitive products. Results will be sent to you shortly.

Further, there are several reasons why the directions for a pediculicide mousse product should specify, "APPLY TO DRY HAIR." These include:

- The anatomy of physiology of *pediculus* (lice) is such that pretreatment with water can decrease the effectiveness of a pediculicide by decreasing the absorption of the formulation containing the active.

- Pediculicides under EPA jurisdiction (prior to FDA Monograph status) specifically stated that all pediculicides should be applied to dry hair.

- Clinical data submitted to the OTC Panel addressed the application of the pediculicide to dry hair. This was reflected in the 1982 "Proposed Pediculicide Monograph" under 358.650 (Labeling of Pediculicide drug products) where it states: "...thoroughly wet with product," implying that the hair is dry to start with.

Additional scientific corroboration for this argument, including literature references, may be found in Attachment 6.

...(The following information is being supplied in response to an 11 February 1999 telephone request from Ms. Rosemary Cook and Ms. Babette Merritt.)...

13. Please send a copy of the quantitative formula for the RID Mousse commercial product.

    The quantitative formula in proper format may be found in Attachment 7. (We had previously included only Master Formula Profiles on pages 554 and 558, and a Batch Record on page 561 of the dNDA.)

14. Please send us a diskette of the RID Mousse labeling.

    The disk is affixed to the copy of this letter going to Babette Merritt. It is formatted in Microsoft Word. Hard copy comprises Attachment 8. Please note the addition of a statement in the Directions section (third bullet) which provides for use of the product on people with long hair.

15. What are the quantitative formulas of other pediculicide products?

    Because we cannot know the quantitative formulas of other companies' preparations we are sending you copies of labels from two competitive products which contain (qualitative) ingredient lists. They are in Attachment 9.

Please call me directly if I can be of further assistance.

Sincerely,

Thomas Blake, R.Ph.
REGULATORY CONSULTANT TO SOLTEC
48 Mt. Olive Road
Budd Lake, NJ 07828
Phone: (973) 347-5129 FAX: (973) 448-0837

mjb
Attachments
cc: Babette Merrit
Document Room (2)

ORIGINAL

NC

235 East 42nd Street
New York, NY 10017-5755
Tel 212 573 1526 Fax 212 573 1186

Pfizer

Consumer Health Care

April 26, 1999

Document Room
Division of Over-The-Counter Drug
Products (HFD-560)
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville, Maryland 20850

Subject: dNDA 21-043 for RID Mousse

Dear Sir/Madam:

As requested by Mr. Thomas Blake, the attached are two (2) copies of the source documents concerning the twelve (12) BanLice adverse drug experiences submitted to you on February 19, 1999 that were provided by our Australian subsidiary.

Sincerely yours,

Charles V. Bainbridge, Pharm.D.
Associate Director, Clinical & Scientific Affairs
Medical Department

CVB/jls
Att.

cc: Thomas Blake

Pfizer Inc
235 East 42nd Street
New York, NY 10017-5755
Tel 212 573 1526 Fax 212 573 1186

ORIGINAL

Pfizer

Consumer Health Care

April 26, 1999

Document Room
Division of Over-The-Counter Drug
Products (HFD-560)
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville, Maryland 20850

[redacted]

BM

Subject: dNDA 21-043 for RID Mousse

Dear Sir/Madam:

As requested by Mr. Thomas Blake, the attached are two (2) copies of the source documents concerning the twelve (12) BanLice adverse drug experiences submitted to you on February 19, 1999 that were provided by our Australian subsidiary.

Sincerely yours,

Charles V. Bainbridge, Pharm.D.
Associate Director, Clinical & Scientific Affairs
Medical Department

CVB/jls
Att.

cc: Thomas Blake

U.S. Food and Drug Administration
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation-III

OTC Consult

To: Linda Hu, M.D., Div. of Over the Counter Drug Products, HFD-560

From: E. Dennis Bashaw, Pharm.D., Div. of Pharmaceutical Evaluation-III, HFD-880 EDB 5/25/99

Through: Arzu Selen, Ph.D., Dep. Dir., Div. of Pharmaceutical Evaluation-III, HFD-880 AS. 5/25/99

Date: 05/25/99

Re: NDA 21-043 Deviation

Overview

At the present time the OTC monograph for pediculocide drug products (21CFR 358.610) lists pyrethrum extract (0.17 to 0.33%) and piperonyl butoxide (2 to 4%) as being effective for the treatment of lice in a **"non-aerosol"** dosage formulation [emphasis added]. The product in question RID Mousse is a topical "hair dressing" which contains 0.33% pyrethrum extract and 4% piperonyl butoxide dispersed in an aerosolized foam. By using a mousse delivery vehicle, it is expected that one would achieve a higher degree of hair shaft coating with the active ingredients via this formulation compared to a shampoo or other liquid dispersal. As aerosolized drug delivery systems are specifically excluded from the OTC monograph, the applicant (Soltec Research, LTD) is planning on submitting their NDA as an NDA deviation under the provisions of 21CFR 330.11 (see Attachment 2). This portion of the regulations allows an OTC manufacturer whose product does not fit under a final monograph to submit an NDA containing only those relevant portions of the NDA that deviate from the final OTC monograph.

As part of the internal review of this filing strategy, a question was referred to the pk team leader assigned to support the Division of Dermatological and Dental Drug Products, as to whether or not in vivo or in vitro pk studies would be needed.

Discussion

This issue was raised with the Division of Pharmaceutical Evaluation Division Director, Dr. John Lazor, by myself for regulatory guidance. From our discussion the following points were identified:

1.) The current OTC monograph does not establish an in vitro or in vivo test for any of the topical pediculocide agents.

2.) There is not an FDA listed reference product for these agents.

3.) We have no record in our review database (reviewer drug files, Excalibur, NDA Drug Files, etc.) of any OTC pediculocide, containing these agents, having conducted an in vivo or in vitro study.

Based on these facts it was decided that as the monograph does not put in place any testing requirement, either for release of drug or in vivo bioavailability, that such a test would not be required. That is to say the lack of an assessment of in vivo bioavailability in this NDA deviation is not a deviation

from the requirements of the final pediculocide monograph and would, therefore, not be required.

HFD-560/DIV File
HFD-560/MO/HU
HFD-560/CSO/Merritt
HFD-880(Bashaw)
HFD-880(Lazor)
HFD-880(drug file)
CDR. ATTN: B. Murphy

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SENT BY FAX 6/1/99

Soltec Research USA
Attention: Thomas Blake, R.Ph.
Regulatory Consult to Soltec
48 Mt. Olive Road
Budd Lake, NJ 07828

Dear Mr. Blake:

Please refer to your pending August 31, 1998 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rid Mousse (pyrethrum extract and piperonyl butoxide) aerosolized foam.

We have completed our review of the chemistry section of your submission and have the following comments and information requests:

1. The Pyrethrum Extract 50% cannot be designated as USP since it does not comply with the current monograph which is specifically for a 20% total level of pyrethrins.

2. In the specifications for Pyrethrum Extract 50%, please include limits of 8.0 to 2.8 for the ratio of pyrethrins I to pyrethrins II. This is the ratio used in the USP monograph for Pyrethrum Extract (20%).

3. The reference standards should be traceable to well characterized materials such as USP reference standards. The practice of using the "lot used in the batch" as the assay standard is discouraged. Please refer to our Guideline for Submitting Samples and Analytical Data for Methods Validation, February 1987.

4. In the manufacturing section, please provide the batch record for Phase C where the two mixtures are filled into the can, sealed and pressurized.

5. In the manufacturing section, please provide the batch record for the packaging procedure.

6. Please confirm which specifications are to be considered regulatory, which are process controls and which are internal specifications for release of the finished product from the filling line. Please provide all specifications for each type of control (in-process, internal release, regulatory, and stability) in a separate table, including those in the Finished Package method IS-924. The current format is very confusing.

7. Foam quality is listed on page 240 as being a Package Lot Specification, however, it is stated that this test is performed before filling the entire batch which makes it an in-process not a release test. This test should be done as a part of the regulatory testing.

8. In the Determination of Foam Quality [redacted]. Specifically determine whether the directions in step 2 of the Procedure section accurately reflect the way the test is run.

9. Please include limits for degradation products in the regulatory/stability specifications for the drug product. Also please provide the methodology to be used.

10. Please provide information showing that the valve components are compatible with the finished drug product.

11. The "significant change interval" and the "standard interval" stability protocols should be in separate tables. The current combined table is confusing.

12. The 1 year at 25°C + 3 months at 40°C test point is not necessary.

13. After the first three commercial batches, the annual stability batches need only follow the 25°C portion of the protocol.

14. Please revise the stability protocol to state that at least one batch per year will be placed in the ongoing stability testing.

15. Please state which site will perform the stability testing for the commercial batches. This site should have a current cGMP rating of acceptable.

16. Nine months of stability data are not sufficient to support a 24 month shelf life. Please submit additional stability data, including statistical analysis of the 25°C data.

17. We remind you that the expiration dating period commences at the time of manufacturing, in this case, the date on which the product is filled into the cans.

18. Please revise the stability protocol to include degradation testing at each time point.

19. Please revise your stability protocol to include foam quality testing at yearly intervals.

20. Please correct the tables in Attachment 2 of the February 19, 1999 amendment. The data in these tables is internally inconsistent.

21. The laboratory methods validation package provided in Volume 2 is incomplete. Please refer to our Guideline for Submitting Samples and Analytical Data for Methods Validation, February 1987 for a listing of items to be included in this document.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

If you have any questions, contact Babette Merritt, Project Manager, at (301) 827-2222.

Sincerely,

/S/

Hasmukh B Patel
Chemistry Team Leader
Division of New Drug Chemistry III
Center for Drug Evaluation and Research

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ON ORIGINAL

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ON ORIGINAL

THOMAS BLAKE, R.Ph.
REGULATORY CONSULTANT TO SOLTEC
48 Mt. Olive Road
Budd Lake, NJ 07828
Phone: (973) 347-5129 FAX: (973) 448-0837

PERSONAL AND CONFIDENTIAL

June 15, 1999

Michael T. Benson, R.Ph., J.D.
Division of OTC Drug Evaluation (HFD-560)
Food and Drug Administration
9801 Corporate Boulevard
Rockville, Maryland 20850

Subject: dNDA 21-043. RID MOUSSE.

Dear Mike:

[redacted]

Additional, untouched copies of the same labeling are included if you want to send them topside. Others are going to the Document Room.

With respect to the Australian professional labeling found in MIMS, the Australian counterpart, I suppose, to our USP-DI, we're learning that the language of concern to the agency--"...use gloves...many applications...wash hands with detergents (as opposed to soap)...avoid food contamination"--were derived from the Australian Department of Agriculture pesticide laws and regulations intended for crop dusters and other personnel who handle bulk insecticides routinely. While not required by the country's pesticide or drug regulations, as promulgated by the Australian Therapeutic Goods Administration (TGA), the professional labeling in question seems to have been embraced by the company's liability lawyers and was not even submitted to the TGA when BanLice was registered.

I'm still waiting for some documentation from Soltec and Pfizer in Australia, but have copies of my E-mail correspondence if you need it.

Finally, the flammability statement may change in the Warning section. It appears that the Australian procedure for flammability testing differs from that required by our Consumer Product Safety Commission (CPSC). The test is being re-done according to the CPSC standard.

As with other statements which the agency may want changed, or require additional information for, perhaps FDA can make these *conditions for approval* in an Approvable Letter, to be addressed with the submission of Final Printed Labeling.

In closing, please tell Charlotte Yasue that we're pretty well buttoned up on responses to her June 1 fax. She'll be receiving my letter shortly. However, we may need your help and hers to address what's going on at USP with respect to the 50% pyrethrum extract issue--you covered it nicely in your August 13, 1998 technical amendment to the pediculicide monograph. I will be calling her as soon as I try my luck with USP.

As always, please call me to discuss this and any other matter.

Very best regards,

Tom

Thomas Blake, R.Ph.

mjb
Enc.

Attachment 1

MEMORANDUM OF TELEPHONE CONVERSATION
Date: July 1, 1999

BETWEEN: Thomas Blake, R.Ph.
Regulatory Consultant to Soltec
48 Mount Olive Road
Budd Lake, NJ 07828
973-347-5129

and Michael T. Benson, R.Ph., J.D.
Regulatory Review Pharmacist (HFD-560)

Subject: Labeling for RID® Mousse

Although recommended labeling had been telefaxed to Mr. Blake, two other changes were determined to be necessary or an improvement as follows:

1. **Ask a doctor before use if you are** allergic to ragweed.
   to
1. **Ask a doctor before use if you have** allergy to ragweed.
   Per 21 CFR 201.66(c)(5)(G)(iv).
   Under 21 CFR 201.66(c)(5)(G)(v), the first version is used only for drug-drug, or drug-food interactions.

2. **Do not use**
   - do not use near the eyes or permit contact with mucous membranes, such as inside the nose, mouth, or vagina, as irritation may occur.

   to

2. **Do not use**
   - near the eyes

   When using this product
   - do not use inside the nose, mouth or vagina. Irritation may occur.

   The labeling is shortened. "Mucous membranes" is not necessarily meaningful to a consumer. The gradation of warnings for each of the named areas is separated according to need for stringency, i.e., the eyes need the stronger warning, and the warning for the nose, mouth and vagina need not be as strong.

I telephoned Mr. Blake to provide him the above described changes. He said that they were fine and he would give that information to the concerned people at Pfizer. Our conversation concluded amicably.

/S/

Michael T. Benson

Consumer Health Care

INTRA-COMPANY CORRESPONDENCE
Technical Services Department
Stability Group

Date: June 16, 1999

To: D. W. Parriott

From: K. L. Lucas

cc: L. Eifler, D. G. Nelson

Subject: **RID Mousse - Data in Support of Tentative Expiration Dating Period**

Six (6) months of satisfactory accelerated stability data from the three (3) Stability/Validation batches of RID Mousse have been submitted with this application in order to project a tentative expiration dating period. All three "pilot" batches were within product specifications after accelerated testing for , thereby providing the basis to apply the common practice of assigning a tentative 24 month expiration date to this product.

Eighteen (18) months of satisfactory long-term data for these 3 batches is also being provided; long-term studies will continue to support this dating period or determine the appropriate expiration date. Prior to the end of this review cycle, twenty-four (24) months of real-time data will be available.

Karen L. Lucas
Stability Coordinator
Technical Services Group

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July 16, 1999

Charles J. Ganley, M.D., Director
Division of Over-the-Counter Drug Products (HFD-560)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, Maryland 20850

Subject: dNDA 21-043. Pediculicide (RID) Mousse

Dear Dr. Ganley:

This responds to your 8 July 1999 Approvable Letter for RID Mousse, specifically to the requirement that we relate our plans for addressing the eighteen conditions for approval within ten days.

All the conditions for approval were addressed in our amendment dated 7 July 1999. Those conditions were essentially the same as the questions and comments from Drs. Hasmukh Patel and Charlotte Yaciw which were faxed to us semi-formally by the latter on 1 June 1999.

We wish to express our thanks to the agency for the preliminary communication, as it allowed us the time to generate and assemble the information requested by the FDA reviewing chemists in anticipation of an action letter. It was another example of the amicable and productive dialogue between FDA and Soltec which has characterized this particular review.

Because the 7 July amendment contained essentially clarifying Chemistry, Manufacturing and Control information, we assume that it will be given a Class I review priority.

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In subsequent communication with the agency, we will address the Prototype Labeling portion of your July 8 letter.

Please call me directly if you have any questions.

Sincerely,

Thomas Blake, R.Ph.
REGULATORY CONSULTANT TO SOLTEC
48 Mt. Olive Road
Budd Lake, New Jersey 07828
Phone: (973) 347-5129 Fax: (973) 448-0837

mjb
Desk copy: Babette Merritt

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Pfizer Consumer Health Care Division
100 Jefferson Road
Parsippany, NJ 07054
EI: 1/6 & 7/99 DJG

SUMMARY OF FINDINGS

This inspection of an OTC drug manufacturer was conducted as a pre-approval inspection for NDA #21-043, RID Mousse Aerosol(Piperonyl Butoxide 4.0%/Pyrethrin 0.33%), assignment #6953. The application provides for finished product release testing and stability testing of RID Mousse. The inspection was conducted in accordance with CP7346.832, Pre-approval Inspections/Investigations.

The previous inspection of 4/22/98 et. al. was conducted as per NWJ-DO FY '98 workplan. The inspection revealed several cGMP deficiencies and was classified "AE".

The current inspection did not appear to reveal any significant deficiencies concerning the testing and control of RID Mousse. Several observations were discussed with firm management during the inspection. No FDA-483 was issued.

A recommendation to approve the subject application was conveyed to firm management at the conclusion of the inspection.

On 1/6/99, I presented my credentials and issued a FDA-482, Notice of Inspection, to Richard C. Norgard, Director, Quality Assurance/Quality Control. R. Norgard is authorized to accept the Notice. A Resources for FDA Regulated Businesses form was also issued to R. Norgard.

Richard Norgard reports to Angelo Santisi, Plant Manager, on a day to day basis. R. Norgard also reports to Jack Hobbs, Vice President, Quality Assurance and Jerry Migliaccio, Vice President, Quality Operations. J. Hobbs and J. Migliaccio are located at Pfizer's corporate headquarters, New York, NY. R. Norgard provided me with current organizational charts.

During the inspection, one or more of the following individuals were present and provided records or information:

Richard Norgard, Director Quality Assurance/Quality Control
Don Parriott, Assoc. Director, Technical Services
Dennis Nelson, Assoc. Director, Research & Development
Luke Foo, Quality Assurance Manager
Christopher Coughlin, Manager, Quality Control
Gary Mcneil, Supervisor, Technical Services
Karen Lucas, Assoc. Analytical Chemist & Stability Coordinator
Shokoohi Maurse, Manger, Quality Control Laboratory
Vince Scaringello, Supervisor, Quality Control Laboratory
Roy Peri, Team Leader, Purchasing/Contract Manufacturing

Soltec Inc., Victoria, Australia, is the NDA holder. Pfizer licensed the rights to develop, manufacture and sell a mousse product in the United States using the Soltec pediculicide mousse technology. Pfizer is responsible for the finished product release testing, batch record review for QA review release and stability testing of RID Mousse. [redacted] is responsible for the manufacture and in-process controls of RID Mousse.

Pfizer Consumer Health Care Division
100 Jefferson Road
Parsippany, NJ 07054
EI: 1/6 & 7/99 DJG

Pre-approval coverage included, but was not limited to, the following areas:

-Laboratory facilities and controls
-Laboratory Investigations
-Change Control for test methods
-Test Method Validation
-Stability data(notebooks & chromatograms)
-CMC Section from NDA
-Relevant SOPs

Inspectional coverage of the above referenced areas did not appear to reveal any significant deficiencies concerning the testing and control of RID Mousse.

Discussion issues with firm management were as follows:

-Demonstrating peak purity of active peaks during forced degradation studies.
-Chromatograms lacked identification.
-Assigning identification numbers for Technical Service investigations.
-Technical Transfer/Qualification of raw material test methods has not been completed.

A recommendation to approve the subject application was conveyed to firm management at the conclusion of the inspection. This recommendation was forwarded to the New Jersey District PAI Manager on 1/8/99.

EXHIBITS

1. Current Organizational Charts, 2pgs

ATTACHMENTS

1. FDA-482 dtd. 1/6/99, 1pg
2. Assignment #6953, 1pg

/S/

Daniel J. Grabicki, Investigator
New Jersey District, NBRP

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July 29, 1999

Charles J. Ganley, M.D., Director
Division of Over-the-Counter Drug Products (HFD-560)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, Maryland 20850

Subject: dNDA 21-043. Pediculicide (RID) Mousse

Dear Dr. Ganley:

This is an amended response to your 8 July 1999 Approvable Letter for RID Mousse, specifically to the requirement that we relate our plans for addressing the eighteen conditions for approval within ten days.

We are amending our original 16 July 1999 letter because, thanks to Ms. Babette Merritt's helpful clarification, we now know that discussion of any labeling issues stand as a Condition for Approval along with the eighteen Chemistry, Manufacturing and Control (CMC) items listed in the Approvable letter.

Though the eighteen CMC issues were addressed in our correspondence of 7 July 1999, we plan to resubmit the information together with any comments we may have on the Prototype Labeling in order to present the agency with a complete package for review.

continued...

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Please call me directly if you have any questions.

Sincerely,

Thomas Blake, R.Ph.
REGULATORY CONSULTANT TO SOLTEC
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Phone: (973) 347-5129 Fax: (973) 448-0837

mjb
Desk copy: Babette Merritt

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September 2, 1999

Charles Ganley, M.D., Director
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Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, Maryland 20850

Subject: dNDA 21-043. Pediculicide (RID) Mousse.
RESPONSE TO THE 8 JULY 1999 APPROVABLE LETTER

Dear Dr. Ganley:

This is a complete response to your 8 July 1999 Approvable Letter for the Pediculicide Mousse. It addresses the 18 Chemistry, Manufacturing and Control (CMC) Conditions for Approval and includes revised labeling which on the whole is in keeping with the agency's critique of our latest proposed labeling, dated 17 June 1999.

Though the CMC portion had been sent to you on 7 July 1999 in anticipation of an Action Letter, it is being resubmitted here in order to have all the issues mentioned in the Approvable Letter addressed in one package. The only changes to our 7 July CMC document are: 1) inclusion of laboratory substantiation for the FLAMMABLE warning and 2) addition of the elements needed for the sampling portion of the Methods Validation section of the dNDA.

For ease of review, we separated the CMC section from the Labeling section. While the Cover Letter contains complete responses to all the issues raised in the Approvable Letter, the attachments appear in the respective sections, preceded by the same **LABELING** or **CMC** portions of this letter. The graphics in the Labeling section are self-explanatory and not paginated.

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Finally, the introductory promotional material (IPM) for RID Mousse has not yet been developed, pending resolution of a few minor labeling issues (see below). When it is prepared, the IPM will conform to approved labeling and be sent in mock-up form to both the OTC Division (HFD-560) and DDMAC (HFD-40) prior to dissemination.

Here, then, are our specific responses to the deficiencies and issues contained within the Approvable Letter:

CHEMISTRY, MANUFACTURING AND CONTROLS

1. The Pyrethrum Extract 50% cannot be designated as USP since it does not comply with the current monograph which is specifically for a 20% total level of pyrethrins.

   We have every expectation that Pyrethrum Extract 50% will be included in a soon-to-be issued USP Monograph. Thanks in part to the agency's prompting, we learned about the mixed and rather protracted compendial history of Pyrethrum Extract in discussion with USP's Dr. Todd Cecil. He explained that revising the current monograph to accommodate Pyrethrum extract 50% was a mere formality, but that he was awaiting certain technical information from [redacted] a major source of the drug. The currently listed Pyrethrum Extract 20% is a simple dilution of Pyrethrum Extract 50%. The technical information which USP requested from [redacted] included: 1) an analytical method to better define the relative concentrations of the [redacted] esters making up Pyrethrum extract, and 2) a true Pyrethrum extract reference standard. If USP receives the information soon, Dr. Cecil explained, a revised monograph for Pyrethrum extract could be included in the next issue of the *Pharmacopeial Forum* (PF).

   [redacted] is Soltec's supplier of the Pyrethrum Extract for the RID Mousse, which is to be marketed by Pfizer. When we contacted [redacted] we received an update on the company's progress with USP's request, including the minutes of a June 30, 1999 meeting between the two parties: 1) a new HPLC method has been developed to resolve [redacted] esters of Pyrethrum Extract. The validation process is completed with trial runs ongoing; 2) using the current [redacted] method, a reference standard is being developed which will include a characterization of the [redacted] esters by HPLC separation techniques; and 3) USP is proposing to reword the present monograph for Pyrethrum Extract to cover the 50% concentration.

At Soltec's and Pfizer's urging, [redacted] is continuing to work with USP to resolve the final remaining issues. ***[N.B. Dr. William Brown is taking over the pyrethrum responsibility from Dr. Todd Cecil.]***

2. In the specifications for Pyrethrum Extract 50%, please include limits of [redacted] for the ratio of pyrethrins I to pyrethrins II. This is the ratio used in the USP monograph for Pyrethrum Extract (20%).

Our raw material specification has been revised to include a test limit of 0.8 - 2.8 for the ratio of pyrethrins I to pyrethrins II. It appears on page 001 of this document.

3. The reference standards should be traceable to well characterized materials such as USP reference standards. The practice of using the as the assay standard is discouraged. Please refer to our Guideline for Submitting Samples and Analytical Data for Methods Validation, February 1987.

Currently there is no adequately characterized USP reference standard available for Pyrethrum Extract (see Item 1). Also, a compendial monograph for piperonyl butoxide does not yet exist, though [redacted] is working with USP to establish one. Because each lot of material is characteristically specific, containing many isomers and esters [redacted] the safest practice at this point is, by default, to employ the as the appropriate assay standard. These assay results are then corrected for the purity of the Pyrethrum Extract used in the batch in order to report a true assay value.

Agreeing with FDA that the practice is not ideal, we will switch to using USP reference standards when they are developed and available. Meanwhile we have taken the agency's advice and have designated a reference standard for piperonyl butoxide and Pyrethrum Extract, attempting for the latter to characterize the relative levels of pyrethrins I and II. Should the exercise prove fruitful, we will modify our test procedures accordingly.

4. In the manufacturing section, please provide the batch record for Phase C where two mixtures are filled into the can, sealed and pressurized.

The four batch records used by [redacted] to implement Phase C may be found on pages 005 to 008. Called [redacted] and [redacted] they record the prefill component checks, then the sequential injection of the [redacted] into the can. The latter worksheet documents the mix, i.e. the finished product. Each worksheet specifies the target and upper and lower control limits. They are simple checklists because the process is automated, not requiring operator instruction.

It is our understanding that these batch records were reviewed without comment by FDA's field staff during its pre-approval inspection of [redacted]

5. In the manufacturing section, please provide the batch record for the packing procedure.

These batch records are the same as those described in Item 4.

6. Please confirm which specifications are to be considered regulatory, which are process controls and which are internal specifications for release of the finished product from the filling line. Please provide all specifications for each type of control (in-process, internal release, regulatory and stability) in a separate table, including those in the Finished Package method IS-924. The current format is very confusing.

The table beginning on page 613, Product Specifications, confirms which specifications and test procedures are to be considered in-process controls, those used for finished product release (a.k.a. regulatory) and which are used for stability testing. At the agency's request, the document has been revised to make Foam Quality testing an in-process control (see Item 7). Finished Package Specifications (IS-924) may be found on page 584 of the dNDA.

The revised Product Specifications table may be found on page 009.

7. Foam quality is listed on page 240 as being a Package Lot Specification; however, it is stated that this test is performed before filling the entire batch which makes it an in-process not a release test. This test should be done as a part of the regulatory testing.

4 pages have been removed here because they contain confidential information that will not be included in the redacted portion of the document for the public to obtain.

Finally, we are including in this CMC section the report of the test, performed according to 16 CFR 1500.43(a), showing RID Mousse to meet the Consumer Product Safety Commission definition of "FLAMMABLE." See pages 069 and 070.

LABELING

In response to the Prototype Labeling you included with the Approvable Letter, we are appending to this section in triplicate a complete set of the graphics for RID Mousse, which consists of a carton, can and consumer information insert. A Spanish version of the latter is also included. For ease of review, we specified the font and type size used for the required Drug Facts panel on the outer package (carton).

We agree with nearly all the agency's revisions, but offer alternatives regarding the following points:

- trade name
- established name
- quantitative ingredient statement
- storage and disposal statement
- can label format
- the RID nit comb

Also, we are amending the labeling to provide for the correct flammability warning, as well as other minor editorial changes. These are discussed under **Other Changes**.

Our responses to the six issues appear below.

Trade Name

The term Lice Killing Mousse is part of the trade name for the product and appears with the registered trademark. The registered trademark is the red stop sign logo bearing the name RID. It is used on all Pfizer's pediculicide/lice treatment products. Use of the full term RID Lice Killing Mousse (in which the name RID appears in the red stop sign logo) therefore distinguishes this product from other Pfizer products in the category (all of which bear the red stop sign logo). It also serves to differentiate this drug product from the many cosmetic-type mousses which are found in the marketplace. Finally, Lice Killing Mousse is a

descriptive term which defines the word pediculicide and that we believe will be readily recognized and understood by consumers. Being consistent, we use the term RID Lice Killing Mousse throughout the product labeling.

Established Name

FDA would have the established name read, "pyrethrum extract (equivalent to 0.33% pyrethrins) and piperonyl butoxide 4% aerosolized foam."

Since there is no official or compendial name for pyrethrum extract and piperonyl butoxide aerosolized foam, and "aerosolized foam" is not a consumer-friendly term, we feel the **established name** requirement of 502(e)(1) of the Food Drug and Cosmetic Act will be met by use of a **common or usual name** on product labeling, as provided by Section 502(e)(3). As with other pediculicides, a statement of product's active ingredient(s) would seem to meet the requirement nicely. Further, the agency's suggested established name appears to be unduly complex and not useful for any purpose other than to fulfill a statutory requirement [see Section 508(c) of the Act].

Therefore, we feel that the statement "pyrethrum extract/piperonyl butoxide" is an appropriate established name. Pediculicide (Lice Treatment) remains as the statement of identity.

Quantitative Ingredient Statement

Rather than being part of the established name, the quantitative statement of active ingredients properly belongs in the Drug Facts panel, as per 21 CFR 201.66(c)(2).

Storage and Disposal Statement

We deleted the storage and disposal statement from the carton left side panel and as per 21 CFR 201.66(c)(5) and (c)(7), and moved it to the Drug Facts panel, where consumers would now expect to find it.

Can Label Format

Though not required, we reproduced for the can all the information from the mandated Drug Facts panel on the carton. Even type size, bolding and use of bullets were preserved.

Because the can is round, the compensatory format is more appropriate.

The RID Nit Comb

Because the nit comb is patented to Pfizer, the company has assigned the RID name to the implement in order to protect it. Further, the name RID appears indelibly on the actual comb which is included in the package. Pointing consumers to the specific implement is not only direct but less confusing.

Other Changes

In the Drug Facts panel, we changed "piperonyl butoxide (4.0%)" to "piperonyl butoxide (4%)" to be consistent with monograph language.

Likewise, we changed "SD Alcohol 3-C (26.50% w/w)" to "SD Alcohol 3-C (26.5% w/w)" because the amount of alcohol in this product is not significant to the last digit shown.

We also moved the Good Housekeeping seal and "plus patented egg removal comb" from the Principal Display Panel (PDP) to the right side panel and, since they did not appear anywhere else on the piece, added the active ingredients to the front of the Consumer Information Insert. Further, we deleted the "Head...Crab...& Body Lice" statement from the PDP. As required, this product indication appears in the Drug Facts panel in accordance with the OTC Monograph [21 CFR 358.650(b)] and the OTC Labeling Rule (21 CFR 201.66). The UPC code will appear in Final Printed Labeling. It will not interfere with the required information.

Finally, RID Mousse was rated "FLAMMABLE" according to recent tests performed according to 16 CFR 1500.43(a). Therefore, the prescribed language, "FLAMMABLE. Keep away from fire or flame" appears under the Warnings heading of the Drug Facts panel. A brief report of the flammability test may be found as the last attachment in the CMC portion of this letter.

With respect to the **"Kills Eggs"** claim which FDA deleted, I had explained in prior telephone conversations with Rosemary Cook and Babette Merritt the existence of a

published study of lice-infected children in Bangladesh[1] which might validate the *in vitro* ovicidal data submitted with our RID Mousse dNDA. However, we have decided to forsake the claim for now, and refrain from sending you the article and attendant information at this time so as not to prolong the agency's review process.

Since much, if not all, of the information in this correspondence would seem to be minor clarifying information, stability update, and non-controversial draft labeling, please confirm that it will be assigned a Class I Review.

As Soltec has now formed a business relationship with Pfizer, Mr. John Tomaszewski and Ms. Dina Russello, regulatory professionals from that company, may be included in our future discussions.

As always, call me directly if you have any questions.

Sincerely,

Thomas Blake
REGULATORY CONSULTANT TO SOLTEC
48 Mt. Olive Road
Budd Lake, NJ 07828
Phone: (973) 347-5129 Fax: (973) 448-0837

mjb
Attachments

APPEARS THIS WAY
ON ORIGINAL

[1] Burgess, et al. "Synergized pyrethrin mousse, a new approach to head lice eradication: efficacy in field and laboratory studies." Clin Therapeutics Vol. 16, No. 1, pages 57-64, 1994.

ORIGINAL NEW CORRESP

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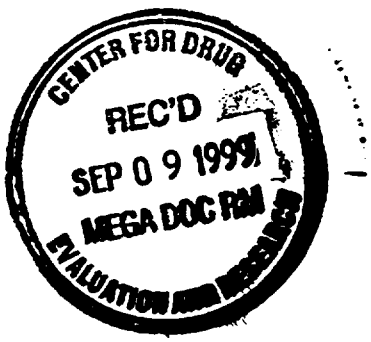

September 8, 1999

Document Room
Division of Over-the-Counter Drug
Products (HFD-560)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, Maryland 20850

Subject: dNDA 21-043. Pediculicide (RID) Mousse
SAMPLE VALIDATION INFORMATION

Ladies/Gentlemen:

Reference is made to Item 18 of the 8 July 1999 Approvable Letter for RID Mousse (dNDA 21-043) and to our complete response dated 2 September 1999. Item 18 called for additional, sample specific information for the METHODS VALIDATION section of the NDA.

In accordance with FDA's February 1987 *Guideline for Submitting Samples* and *Analytical Data for Methods Validation*, we are sending you, in quadruplicate, the requested information. It is an exact reproduction of pages 47-68 of the 2 September document, which was our response to Item 18 of the Approvable Letter. It consists of the following sample-specific information:

	Pyrethrum Extract	Piperonyl Butoxide	Finished Product
1. Sample quantities			
2. Lot Nos.			
3. Certificates of Analysis			
4. Material Safety Data Sheets			**Pfizer (page 62)**

Please call me directly if you have any questions.

Sincerely,

Thomas Blake

Thomas Blake, R.Ph.
REGULATORY CONSULTANT TO SOLTEC
Phone: (973) 347-5129 Fax: (973) 448-0837

mjb
Attachments

APPEARS THIS WAY
ON ORIGINAL

U.S. Pharmacopeia
The Standard of Quality

12601 Twinbrook Parkway
Rockville, MD 20852

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1/3

October 6, 1999

[redacted]

Your letter dated: 07/08/99

Title: PYRETHRUM EXTRACT
Subject: Definition and Assay

Dear Mr. Essig:

Members of the relevant USP Subcommittee, following consideration of the referenced subject, have finalized and approved a revision proposal for the title item. Arrangements are being made accordingly to publish a proposed revision for public comment. This will appear in a future number of Pharmacopeial Forum; we will notify you of the number of PF during the editorial stage. In the absence of significant adverse comment, and if no further need for additional data or information is identified during the public review period, the issue will be presented to the USP Committee of Revision for possible official adoption. We will keep you apprised of such progress.

Sincerely,

William E. Brown

William E. Brown
Senior Scientific Associate
Division of Standards Development

DSD FAX: (301) 816-8373

BEST POSSIBLE COPY

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November 1, 1999

Document Room
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Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, Maryland 20850

Subject: dNDA 21-043. RID MOUSSE.

Ladies/Gentlemen:

Attached is a 6 October 1999 letter from USP which is pursuant to Item 1 of our 2 September 1999 Response to FDA's 8 July 1999 Approvable Letter for RID Mousse.

USP indicates that the 50% Pyrethrum Extract used in RID Mousse has entered the Compendial process for becoming official.

Please call me directly if you have any questions.

Sincerely,

Thomas Blake

Thomas Blake, R.Ph.
REGULATORY CONSULTANT TO SOLTEC
Phone: (973) 347-5129 Fax: (973) 448-0837

mjb
Attachment

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FAX COVER SHEET

Pages Including This Cover Sheet: 3

Date: 1 November 1999

To: **BABETTE MERRITT**
Division of OTC Drug Products (HFD-560)

Phone: (301) 827-2301

Fax: 301-827-2315

Subject: dNDA 21-043. RID MOUSSE

—MESSAGE—

Dear Babette,

Please pass on to Charlotte this letter from USP which indicates that the 50% Pyrethrum Extract is on its way to becoming official.

Three copies are on their way to the Document Room.

Best regards,

Tom Blake

APPEARS THIS WAY
ON ORIGINAL

—CONFIDENTIAL—

ORIGINAL

ORIG AMENDMENT

BC

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November 10, 1999

Charles Ganley, M.D., Director
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Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, Maryland 20850

Subject: dNDA 21-043. Pediculicide (RID) Mousse.
ADDITIONAL RESPONSE TO THE 8 JULY 1999 APPROVABLE LETTER

Dear Dr. Ganley:

This responds to the Chemists' comments which we received by fax from Ms. Babette Merritt on 2 November 1999 and which she addressed by phone two days later. The comments were specific to Soltec's 2 September 1999 Response to FDA's 8 July 1999 Approvable Letter for RID Mousse (dNDA 21-043).

Here, then, are Soltec's responses to FDA's 2 November fax:

1. *Please delete the "USP" designation for Pyrethrum extract, 50%. This ingredient is not covered by the monograph as published in either USP 23 or USP 24. This material cannot be called "USP" until a USP monograph covering the 50% extract is implemented. Revisions do not become official until they are formally incorporated into the USP, usually by inclusion in a supplement to the current volume. Note that proposed revisions to the USP published in the Pharmacopeial Forum are for discussion only and subject to change. A significant number of these are never implemented.*

   We are deleting the USP designation for the Pyrethrum extract 50% in all of Soltec's and Pfizer's working documents. Additionally, we have instructed [redacted] of the active ingredient, and [redacted] the manufacturer, to do the same. The official designation will be reinstated and USP monograph requirements met when Pyrethrum extract becomes official at the 50% concentration.

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2. *The container compatibility information provided (Item 10) is not adequate. Please provide the following additional information:*

   a. *The complete reports for the studies summarized in the memo dated July 7, 1999.*

   Attached are the complete reports for the studies summarized in the memo dated July 7, 1999 (page 018-019 of our 2 September amendment). The July memo is appended to this letter for convenience.

   Pages 01-02 report the findings from the tests for about The report also lists the results of a Test--also used for commercial batches--conducted on cans stored for around . Results from all three tests were rated acceptable.

   Pages 04-12 contain the raw data for the Test. Ten cans from each of the three stability lots were weighed at 30, 60 and 90 days Since they represent a worse case scenario, only the 90 day results are reported here. Weight loss was minimal, not exceeding which is typical for aerosol containers and well within the range of the target fill weight (see 2d below).

   Though not specifically requested by the agency, but relevant to Comment 2b (below), we are including on pages 13-16 the report of a Packaging Compatibility study performed after 90 days Ten cans from each of the three stability lots at each temperature were opened and evaluated. Any imperfections were minor and judged to be acceptable.

   b. *The complete report for the study on the study on the weight loss and visual compatibility after 90 days at 50 °C.*

   The complete study on weight loss was referenced in Item 2a and may be found on pages 04-12 of this document. No visual inspections were performed on samples stored at 50°C, but were conducted on those stored for 90 days as reported here on pages 13-16.

c. *Methods IT-1057 and IT-1036 used to generate the data summarized in the July7, 1999 memo.*

Methods IT-1057 and IT-1036 may be found on pages 17-18 and 19-20, respectively, of this document. Method IT-1032 (Unit Pressure Test for Aerosol Products), since it relates to the findings reported in 2a above, is included on page 21.

d. *The criteria used to determine the acceptability of the data, i.e., the expected value ranges for the delivery rate, dispensed weight and weight loss.*

Three points are relevant to this request. First, delivery rate and dispensed weight have no clinical significance, as there is no fixed dose for topically applied pediculicide drugs. Second, the three tests that were part of the initial stability program were conducted largely to measure consistency, i.e., to identify obvious product failures (none were found). Third, changes affecting commercial drug product/container compatibility would be picked up by other tests which, at the agency's behest, were incorporated into our ongoing stability program. Such tests include those for Filled Unit Pressure (IT-1032), Foam Quality (TP-482) and Determination of External Peaks (Operating Procedure 2355).

With those three precepts in mind, we would like to address the criteria issue as follows:

DELIVERY RATE. There is no industry standard for delivery rate of a continuous valve topical aerosol. We checked with USP, ASTM, CSMA and CHPA, all of whom explained that a standard would be impractical due to these products' many uses and valve configurations. Intended use, practicality and consumer acceptance appear to be the sole criteria for the delivery rate of topical aerosol products. These were the criteria we used. As explained above, the Delivery Rate Test for RID Mousse was conducted to determine consistency among the cans tested. No significant fluctuations were seen.

For commercial batches, discrepancies in delivery rate would be detected by the Filled Unit Pressure and Foam Quality tests (pages 21 ad 22, respectively) which are part of the RID Mousse ongoing stability program.

DISPENSED WEIGHT. The criterion used for dispensed weight was virtually the declared net contents of the can. It is also the finished product release specification for commercial batches. During the initial stability tests,

results of the dispensed weight tests were judged to be acceptable.

WEIGHT LOSS. A weight loss below label claim and substantially less than the original fill weight was considered unacceptable. Though the net contents of the can are labeled 156g, the target fill weight for commercial batches is
since it is customary to overfill products of this nature. [See 21 CFR 201.62(q) which permits reasonable variations from label claim.] Weight loss during the initial stability test never deviated more than
This was a variation well within the range of the target fill weight.

Please call me directly if you have any questions.

Sincerely,

Thomas Blake, R.Ph.
REGULATORY CONSULTANT TO SOLTEC
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mjb
Attachments

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RECEIVED
FEB 3 2000
By dyp

January 27, 2000

Charles Ganley, M.D., Director
Division of Over-the-Counter Drug
Products (HFD-560)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, Maryland 20850

Subject: **NDA 21-043.** LABELING FOR RID MOUSSE.
Response to FDA's 5 Jan. 2000 Faxed Memo

Dear Dr. Ganley:

Reference is made to the FDA's January 5, 2000 faxed memo containing the Reviewer's comments on the labeling for RID Mousse, NDA 21-043, and to our January 14, 2000 faxed memo to Ms. Rosemary Cook and Ms. Babette Merritt.

We commit to making all the changes requested by the agency, Items 1 to 3 in FDA's January 5, 2000 memo.

We will send you a complete, revised set of color graphics as soon as it is composed.

As always, please call me if you have any questions.

Sincerely,

Thomas Blake

Thomas Blake, R.Ph.
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mjb
cc: Babette Merritt

Given to C. Racin 2/7/00

THOMAS BLAKE, R.Ph.

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FAX COVER SHEET

Pages Including This Cover Sheet: 4

Date: 7 February 2000

To: **BABETTE MERRITT**
THOMAS PARMELEE
Division of OTC Drug Products (HFD-560)

Phone: (301) 827-2301
Fax: (301) 827-2315

Subject: **dNDA 21-043. RID MOUSSE**

—MESSAGE—

Dear Babette and Tom,

Appreciating that the Chemist's heavy workload may have caused her to inadvertently miss an entry in the latest *Pharmacopeial Forum*, we are faxing these three pages from that publication which are pertinent to RID Mousse. They show genuine progress being made in our efforts to make official the 50% Pyrethrum Extract: the appropriate proposed monograph begins on page 202. Please pass it on to Charlotte.

If she has seen it already, then accept our apologies for the redundancy and professional congratulations for her ability to keep up with the literature.

Best regards,
Tom

—CONFIDENTIAL—

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February 14, 2000

Charles Ganley, M.D., Director
Division of Over-the-Counter Drug
Products (HFD-560)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, Maryland 20850

Subject: NDA 21-043. RID MOUSSE
LABELING

Dear Dr. Ganley:

Reference is made to our 31 January 2000 amendment and 11 February 2000 telephone conversation with Mr. Thomas Parmelee in which he pointed out two small discrepancies in the DRUG FACTS section of the RID Mousse labeling.

The two discrepancies were: 1) in the Active Ingredient line, the term "calculated without propellant" should be in the same font as the adjacent words, and 2) under "Questions," the word "call" should not be bolded.

The corrections have been made. They appear in the enclosed proposed draft labeling. As agreed with Mr. Parmelee, we are sending you copies of the black and white graphics. If you agree that this RID Mousse labeling is acceptable, our next such submission to you will be the Final Printed Labeling.

Please call me if you have any questions.

Sincerely,

Thomas Blake, R.Ph.
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Thomas Parmelee

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March 1, 2000

Charles J. Ganley, M.D., Director
Division of Over-the-Counter Drug Products (HFD-560)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, Maryland 20850

Subject: NDA 21-043. Rid Mousse
LABELING

Dear Dr. Ganley:

As requested by Messrs. Thomas Parmelee and Michael Benson on March 1, 2000, this will verify that the type size (8-point) and font used for the entire Active Ingredients heading are the same as those used for the other headings in the Drug Facts portion of the outer package labeling for RID Mousse. The other headings are, of course, "Uses," "Warnings," "Directions," etc.

Please call me directly if you have any questions.

Sincerely,

Thomas Blake, R.Ph.
REGULATORY CONSULTANT TO SOLTEC
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Budd Lake, New Jersey 07828
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mjb
cc: Mike Benson
Tom Parmelee
Document Room

CENTER FOR DRUG EVALUATION AND RESEARCH
FOOD AND DRUG ADMINISTRATION

FACSIMILE TRANSMISSION RECORD

DATE: March 2, 2000

FROM: Thomas A. Parmelee, Pharm.D.
Division of OTC Drug Products, HFD-560

PHONE: 301-827-2271 FAX: 301-827-2315

TO: Tom Blake, R.Ph.
Soltec
973-448-0838 FAX: 973-448-0837

No. Of Pages (including cover) ____

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Message:

Please submit a letter of commitment immediately, which states that the following serves as the approved labeling for NDA 21-043:

1) the carton label and immediate container (can) label contained in your submission dated February 14, 2000
2) the Consumer Information Insert contained in your submission dated January 31, 2000

In addition, please commit to the following:

1) submit twenty (20) copies of Final Printed Labeling (FPL) that is identical to the approved draft labeling for NDA 21-043
2) remove the word "new" from the carton, immediate container, and any other labeling for this product six (6) months after initial marketing.
3) ensure the accuracy of the Spanish translation of the Consumer Information Insert to be identical to the approved Consumer Information Insert.

The User Fee goal date for this supplemental new drug application is March 7, 2000.

If you have any questions, please contact Thomas A. Parmelee, Pharm.D., Regulatory Project Manager, at 301-827-2271.

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March 3, 2000

Charles J. Ganley, M.D., Director
Division of Over-the-Counter Drug Products (HFD-560)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, Maryland 20850

Subject: NDA 21-043 for RID Mousse
Commitment Letter

Dear Dr. Wilkin:

This responds to the fax which was sent to us at 11:25 a.m., Friday, March 3, 2000 by Dr. Thomas Parmelee. The communication asked us to make certain commitments for RID Mousse (NDA 21-043). They are, *in toto*:

1. The RID Mousse carton label and immediate container (can) labeling contained in our February 14, 2000 submission will not be changed, and will serve as the approved labeling for the new product;

2. Likewise, the Consumer Information Insert of January 31, 2000 will appear unchanged within packaging for the commercial product;

3. Soon after FDA approval of RID Mousse, we will submit 20 copies of the Final Printed Labeling (FPL) which is identical to the draft labeling for NDA 21-043 as discussed above;

4. The word "new" will be removed from all RID Mousse product labeling 6 months after initial marketing;

5. We will provide certification that the Spanish translation of the Consumer Information is identical to the English (American) version.

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Please call me directly if you have any questions.

Sincerely,

Thomas Blake, R.Ph.

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Copies: Babette Merritt
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March 4, 2000

Charles J. Ganley, M.D., Director
Division of Over-the-Counter Drug Products (HFD-560)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, Maryland 20850

Subject: NDA 21-043 for RID Mousse
Commitment Letter

Dear Dr. Ganley:

This responds to the fax which was sent to us at 11:25 a.m., Friday, March 3, 2000 by Dr. Thomas Parmelee. The communication asked us to make certain commitments for RID Mousse (NDA 21-043). They are, *in toto*:

1. The RID Mousse carton label and immediate container (can) labeling contained in our February 14, 2000 submission will not be changed, and will serve as the approved labeling for the new product, with two inconsequential exceptions.
   First, the word "new" will not appear on the can label. Since the term is not seen by consumers at point-of-purchase, it serves no useful purpose.
   Second, the lot number and expiration date have been moved from the can label to the bottom of the can because recently it was determined that the packaging machinery could print only on the can bottom. Consequently, that portion of the can label on which "Lot" and "Exp" once appeared now bears the following statement: "For Lot No. and Exp. Date see bottom of can".

   The slightly revised labeling is attached.. Nothing else has changed on either the can or carton label.

2. Likewise, the Consumer Information Insert of January 31, 2000 will appear unchanged within packaging for the commercial product;

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3. Soon after FDA approval of RID Mousse, we will submit 20 copies of the Final Printed Labeling (FPL) which is identical to the draft labeling for NDA 21-043 as discussed above;

4. The word "new" will be removed from the RID Mousse carton labeling 6 months after initial marketing. As discussed in Item 1 above, the term does not appear on the can label (or Consumer Information Insert).

5. We will provide certification that the Spanish translation of the Consumer Information Insert is identical to the English (American) version.

Please call me directly if you have any questions.

Sincerely,

Thomas Blake, R.Ph.
REGULATORY CONSULTANT TO SOLTEC
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March 7, 2000

Charles J. Ganley, M.D., Director
Division of Over-the-Counter Drug Products (HFD-560)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, Maryland 20850

Subject: NDA 21-043 for RID Mousse
Commitment Letter

Dear Dr. Ganley:

This responds to the fax which was sent to us at 2:25 p.m., Thursday, March 7, 2000 by Dr. Thomas Parmelee. The communication asked us to commit to making the following changes to the Drug Facts portion of the carton labeling for RID Mousse:

> Under the heading "Active Ingredients (calculated without propellant) Purpose," the "L" in Lice treatment should be in upper-case.

We commit to making the changes exactly as FDA requested as a condition for approval of NDA 21-043 for RID Mousse. The modification applies to both terms, "Lice treatment" in the aforementioned labeling section. We are implementing the change immediately.

Please call me directly if you have any questions.

Sincerely,

Thomas Blake, R.Ph.
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Dr. Thomas Parmelee
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CENTER FOR DRUG EVALUATION AND RESEARCH
FOOD AND DRUG ADMINISTRATION

FACSIMILE TRANSMISSION RECORD

DATE: March 7, 2000

FROM: Thomas A. Parmelee, Pharm.D.
Division of OTC Drug Products, HFD-560

PHONE: 301-827-2271 FAX: 301-827-2315

TO: Tom Blake, R.Ph.
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No. Of Pages (including cover) 2

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Message:

Please submit a letter of commitment immediately that you will implement the following labeling change as a basis of approval for NDA 21-043:

Under the "Active Ingredients (calculated without propellant) Purpose", the "L" in Lice treatment should be in upper-case.

The User Fee goal date for this supplemental new drug application is March 7, 2000.

If you have any questions, please contact Thomas A. Parmelee, Pharm.D., Regulatory Project Manager, at 301-827-2271.

cc: Original NDA 21-043
HFD-560/Div. File
HFD-560/Parmelee/Cook/M.Chang/Benson/Hu

SUPPORTING DOCUMENTS:

Type/Number	Subject	Holder	Status	Review Date	LOA Date
Type II	manufacturer		NA	NA	1/27/98
Type III			adequate	4/7/99	5/18/98

RELATED DOCUMENTS (if applicable): None

CONSULTS: None initiated by chemistry.

REMARKS:

The OTC monograph for this pediculicide (21 CFR 358.610) specifically excludes aerosolized dosage forms, therefore, this NDA was submitted under 21 CFR 330.11 (deviations from a final monograph) which only requires that the portions deviating from the monograph be included in the NDA. Consequently the drug substance section is very brief since these are covered in the monograph.

The drug product is an aerosolized foam, in this case a solution emulsified with a propellant. It delivers a thick creamy mass about the consistency of shave cream and is packaged and dispensed in a similar manner. The product does not contain any component which would mask the fact that the foam has a distinct pesticide-like odor. It is classed as an aerosol because it contains a propellant and is filled into a pressurized container (see the CDER Data Standards Manual definitions for Dosage Forms). Testing for airborne particulates is not done on this type of product. Note that a number of documents in this submission are on Pfizer letterhead.

CONCLUSIONS & RECOMMENDATIONS:

The deficiencies identified in this review should be sent to Soltec either in a discipline letter or an Approvable letter.

/S/

Charlotte Yaciw, Review Chemist, HFD-830/550

/S/ SPS 7/9/99

Hasmukh B. Patel, Team Leader, HFD-550