CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74726

CORRESPONDENCE

ANDA 74-726

Upsher-Smith Laboratories, Inc.
Attention: Mark S. Robbins, Ph.D.
14905 23rd Avenue North
Minneapolis, MN 55447

AUG 28 1995

Dear Sir:

Please refer to your abbreviated new drug application (ANDA) dated August 8, 1995, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Potassium Chloride Extended-release Tablets USP, 20 mEq.

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to file this ANDA under 21 CFR 314.101(d)(3) for the following reason:

> You have failed to address the method of use patent, U-99 (method of providing potassium to a subject in need of potassium), #4863743, expiring September 5, 2006, for the reference listed drug. Please revise your patent certification to reflect the current information in Approved Drug Products with Therapeutic Equivalence Evaluations, 15th edition.
>
> While we note that you provided a bioequivalence study for your 20 mg strength, an in vivo bioequivalence waiver cannot be granted for your strength under 21 CFR 320.22(d)(2)(iv) which excludes controlled release dosage forms from the in vivo waiver request provision.

Thus, it will not be filed as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

In addition, we note that you state in your cover letter that a field copy of the application "is being submitted" to the district office. Please provide a revised certification with an original signature stating that a field copy **has been** sent to the district office and that the third (field) copy is a "true" copy of the technical sections of the application.

Within 30 days of the date of this letter you may amend your application to include the above information or request in writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If after the informal conference, you still do not agree with our conclusion, you may make a written request to file the application over protest, as authorized by 21 CFR 314.101(c). If you do so, the application shall be filed over protest under 21 CFR 314.101(b). The filing date will be 60 days after the date you requested the informal conference. If you have any questions please call:

William Russell
Consumer Safety Officer
(301) 594-0315

Sincerely yours,

/S/

Jerry Phillips
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 74-726
cc: DUP/Jacket
Division File
HFD-82
Field Copy
HFD-600/Reading File
HFD-615/MBennett

ANDA Refuse to File!

ANDA 74-726

Upsher-Smith Laboratories, Inc.
Attention: Mark S. Robbins, Ph.D.
14905 23rd Avenue North
Minneapolis, MN 55447

OCT 3 1995

Dear Sir:

Please refer to your abbreviated new drug application (ANDA) dated August 8, 1995, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Potassium Chloride Extended-release Tablets USP, 20 mEq.

Reference is also made to our "Refuse to File" letter dated August 28, 1995, and your amendment dated September 11, 1995.

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to file this ANDA under 21 CFR 314.101(d)(3) for the following reason:

> We acknowledge your comments regarding your request for a waiver of *in-vivo* bioequivalence for potassium chloride extended-release tablets USP, mEq. However, the regulations under 21 CFR 320.22(d)(2)(iv) and the current policy of the Division of Bioequivalence require *in-vivo* bioequivalence studies for each strenth of an extended-release tablet. Please refer to the Guidance, Oral Extended (Controlled) Release Dosage Forms, *In Vivo* Bioequivalence and *In Vitro* Dissolution Testing, dated September 9, 1993, for information regarding study requirements for extended-release tablets.

Thus, it will not be filed as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

Within 30 days of the date of this letter you may amend your application to include the above information or request in writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If after the informal conference, you still do not agree with our conclusion, you may make a written request to file the application over protest, as authorized by 21 CFR 314.101(c). If you do so, the application shall be filed over protest under 21 CFR 314.101(b). The filing date will be 60 days after the date you requested the informal conference. If you have any questions please call:

William Russell
Consumer Safety Officer
(301) 594-0315

Sincerely yours,

/S/ 10/3/95

Jerry Phillips
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 74-726
cc: DUP/Jacket
Division File
HFD-82
Field Copy
HFD-600/Reading File
HFD-615/MBennett

ANDA 74-726

Upsher-Smith Laboratories, Inc.
Attention: Mark S. Robbins, Ph.D.
14905 23rd Avenue North
Minneapolis, MN 55447

OCT 30 1995

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to our "Refuse to File" letters dated August 28, 1995, and October 3, 1995; and your amendments dated September 11, 1995, and October 12, 1995.

NAME OF DRUG: Potassium Chloride Extended-release Tablets USP, 20 mEq

DATE OF APPLICATION: August 8, 1995

DATE OF RECEIPT: August 10, 1995

DATE ACCEPTABLE FOR FILING: October 13, 1995

We will correspond with you further after we have had the opportunity to review your application.

Please identify any communications concerning this application with the number shown above.

Should you have questions concerning this application contact:

Jim Wilson
Consumer Safety Officer
(301) 594-0310

Sincerely yours,

/S/ 10/30/95

Jerry Phillips
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 74-726

Upsher-Smith Laboratories, Inc.
Attention: Mark S. Robbins, Ph.D.
14905 23rd Avenue North
Minneapolis, MN 55447

MAR 27 1996

Dear Sir:

This is in reference to your abbreviated new drug application dated August 8, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Potassium Chloride Extended-release Tablets USP, 20 mEq.

Reference is also made to your amendment dated October 12, 1995.

The application is deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

A. Chemistry Deficiencies

1. The DMF you referenced for the drug substance chemistry manufacturing and controls (CMC) information is a DMF. Please provide a letter of authorizat for the DMF describing the manufacturing, purification, testing and packaging procedures for drug substance. Alternatively, this information m submitted to the application by you.

2. No information is provided in reference to the corrugated shipping container use for the bulk pa of tablets. Please respond to the followin

   a. Please provide information regarding the mat of construction and regulatory status for th components of the corrugated shipping container.

   b. Please provide test data indicating the container closure system provides an adequate barrier for this product. Specifically, the container must meet the permeability and resealability requirements for tight containers.

   c. Please provide information regarding the resealing procedures for this container. Please be informed that twist ties are generally not considered to be adequate for reproducible resealing.

Bio review

d. Please provide information regarding the intended purpose for these containers. If they are to be shipped to a repackager, we require evidence of an agreement to use appropriate market packaging materials.

3. In reference to the coated granule release specifications, please respond to the following:

a. The dissolution specification is much wider than the data you provided from 38 different granulation production batches. Please revise the specification to more closely characterize the manufactured material.

b. Please perform the methanol residue test as a routine in-process control with a limit specification characteristic of the data provided (about 50 ppm). Once enough data is available for post approval batches a supplement may be provided to discontinue this test.

4. In reference to the stability information, please respond to the following:

a. The stability data for the bulk container of tablets in doubled polyethylene bags does not indicate that the bags were protected only by the shipping carton. Specifically, were the bags directly exposed to the humidity?

b. The stability report provides average results for the dissolution data, but the USP specification is based on individual results. Please provide the high and low dissolution results in the stability reports.

c. The stability specification is different from the release dissolution specification. The specification for stability is the single time point USP dissolution specification. Please revise the stability dissolution specification to be the same as the release dissolution specification.

d. The post approval stability commitment indicates that % of the production batches will be tested annually while on stability. Upsher-Smith should commit to place at least one batch on stability each year and to test them at 0, 3, 6, 9, 12, 18, and 24 months.

5. The particle size specification for the Potassium Chloride USP raw material is too broad. The amount

retained on the screen is specified as NLT %. The data indicate that the biobatch was manufactured with a batch that had % retained on the screen. Please revise the screen specification to more closely match the material that was used in the biobatch.

B. Labeling Deficiencies

1. CONTAINER:

a. 100's, 500's and 1000's

i. Front Panel

Revise "20 mEq" to read "20 mEq K".

ii. Side Panel

Each ... 1500 mg potassium chloride equivalent to (20 mEq of potassium).

b. Unit-Dose blister

Satisfactory in draft.

2. CARTON: Unit-Dose 100's

a. See comments under Container.

b. Include a statement as to whether or not the unit-dose package is child-resistant. If it is not child-resistant, we encourage the inclusion of a statement that if dispensed to outpatients, it should be with a child resistant container. For example:

This unit-dose package is not child-resistant. If dispensed for outpatient use, a child-resistant container should be utilized.
[Note: The second sentence is optional].

3. INSERT

a. GENERAL COMMENTS

i. Your proposed proprietary name "Klor-Con®M20" will be forwarded to the CDER Labeling and Nomenclature Committee for review and comment. We defer final comment on your proposed proprietary name pending notification of the Committee's findings.

ii. Throughout the text of the insert use the

term "extended-release rather than "controlled release" or "sustained release".

b. DESCRIPTION

Include the molecular weight, 74.55.

c. PRECAUTIONS

i. General

Use italic print for "*per se*". [two places]

ii. Drug Interactions

Use italic print for "*in vitro*".

iii. Pregnancy

Please note "*Pregnancy*" is the subsection heading. Revise to read:

Pregnancy: Pregnancy Category C: Animal reproduction ...

iv. Pediatric Use

... pediatric patients have not ...

d. OVERDOSAGE

... dextrose injection containing ... [replace "solution" with "injection"]

e. DOSAGE AND ADMINISTRATION

i. Paragraph 3 -

Each Klor-Con®M20 extended-release table provides 1500 mg of potassium chloride and 20 mEq potassium.

ii. Last paragraph -

... Klor-Con®M20 extended-release tablet that is not ...

f. HOW SUPPLIED

i. Klor-Con®M20 Extended-release tablets, 1500 mg of potassium chloride (20 mEq of potassium) are ...

Please revise your labels and labeling, as instructed above, and submit in final print. Please note that we reserve the right to request further changes in your labels and labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered a MAJOR amendment and should be so designated in your cover letter. You will be notified in a separate letter of any deficiencies identified in the bioequivalence portion of your application. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

/S/ 3/27/96

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 74-726
Dup File
Division File
Field Copy
HFD-600/Reading File
HFD-82

NOT APPROVABLE MAJOR

ANDA 74-726

Upsher-Smith Laboratories
Attention: Mark Halvorsen, Pharm.D.
14905 23rd Avenue North
Minneapolis MN 55447-4709

MAR - 3 1997

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Potassium Chloride Extended Release Tablets USP, 20 mEq, and to the additional *in vitro* data submitted February 12, 1997, regarding the comparative dissolution for the half tablets.

1. The Division of Bioequivalence has completed its review of this material, and has no further questions at this time.

2. The *in vitro* test results on half tablets are acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability programs. The dissolution testing should be conducted in 900 mL of deaerated water at 37° C using USP 23 apparatus 2 (Paddle) at 50 rpm. The test should meet the following specifications:

1 hour				NMT	%
2 hours	NLT	%	and	NMT	%
6 hours	NLT	%	and	NMT	%
12 hours	NLT	%			

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/S/

Rabindra Patnaik, Ph.D.
Acting Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Called 4/15/99 talked to Michael Poirier, informed that Upsher-Smith has not started marketing, their boss will call me back. JAN 28 1999 4/15/99

ANDA 74-726

Upsher-Smith Laboratories, Inc.
Attention: Mark B. Halvorsen, Pharm.D.
14905 23rd Avenue North
Minneapolis, MN 55447-4709

Dear Sir:

On November 20, 1998, Upsher-Smith Laboratories, Inc. received approval for your abbreviated new drug application (ANDA) for KLOR-CON M20 (Potassium Chloride Extended-release Tablets USP, 20 mEq). The purpose of this letter is to clarify the 180-day exclusivity provisions under the Federal Food, Drug, and Cosmetic Act with respect to your application. In light of the recent court decisions in Granutec v. Shalala, and Mova v. Shalala, including the district court's order of June 1, 1998 in Mova, declaring the "successful defense" requirement of 21 C.F.R. 314.107(c)(1) invalid, and directing FDA not to enforce it, FDA is reinterpreting Section 505(j)(5)(B)(iv). On November 5, FDA published an interim rule deleting the "successful defense" requirement from 21 CFR 314.107(c)(1).

Upsher-Smith Laboratories, Inc. was the first applicant to submit a substantially complete ANDA with a Paragraph IV Certification for the drug product noted above. The listed drug product referenced in your application is subject to a period of patent protection which curently expires on September 5, 2006, (patent 4,863,743). Your application contains a patent certification under Section 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug, and Cosmetic Act (Act) stating that your manufacture, use, or sale of this drug product will not infringe on the patent or that the patent is otherwise invalid. You subsequently informed the Agency that Key Pharmaceuticals, Inc. initiated a patent infringement suit against you in the United States District Court for the District of New Jersey (Key Pharmaceuticals, Inc. v. Upsher-Smith Laboratories, Inc., Civil Action No. 95-6281 [WHW]). You have also notified the Agency that on July 24, 1997, the New Jersey court issued a Stipulation and Order of Dismissal terminating the litigation with Key Pharmaceuticals, Inc.

As noted above, Upsher-Smith Laboratories, Inc. was the first applicant to submit a substantially complete ANDA with a paragraph IV certification. Therefore, you are eligible for 180-days of market exclusivity for this drug product. Such exclusivity will begin to run either from the date Upsher-Smith Laboratories, Inc. begins commercial marketing of this drug product, or from the date of a decision of a court finding the patent invalid or not infringed, whichever occurs earlier [Section 505(j)(5)(B)(iv)]. A court decision that can trigger the beginning of exclusivity is a decision of any court in a patent infringement action resulting from a Paragraph IV Certification in which the court finds that the patent is invalid or not infringed. In a case such as yours where the case involving the first applicant was dismissed by order of the court, a subsequent court decision could be rendered in a case involving a subsequent ANDA applicant. With respect to the "first commercial marketing" trigger for the commencement of exclusivity, please refer to 21 C.F.R. 314.107(c)(4). The Agency expects that you will begin commercial marketing of this drug product in a prompt manner.

If you have additional questions concerning the effective date of approval of an abbreviated new drug application and the Agency's elimination of the requirement that an ANDA applicant successfully defend a patent infringement suit to be eligible for 180-days of marketing exclusivity, please refer to the interim rule published in the November 5, 1998 Federal Register (Volume 63, No. 214, 59710) or contact Mr. Donald Hare, Special Assistant to the Director, at (301) 827-5845.

Sincerely yours,

/S/ 1/28/99

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 74-726

Upsher-Smith Laboratories
Attention: Diane Gibbs
14905 23rd Avenue North
Minneapolis MN 55447-4709

SEP - 6 1996

Dear Madam:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Potassium Chloride Extended Release Tablets USP, 20 mEq, and to the additional *in vitro* data submitted June 20, 1996.

1. The Division of Bioequivalence has completed its review of this material, and has no further questions at this time.

2. The following dissolution testing will need to be incorporated into your stability and quality control programs:

   Testing should be conducted on 12 individual dosage units each of the test and reference products in 900 mL of deaerated water at 37°C using USP 23 apparatus 2 (Paddle) at 50 rpm. The products should meet the following specifications:

1 hour			NMT	%
2 hours	NLT	%	and NMT	%
6 hours	NLT	%	and NMT	%
12 hours	NLT	%		

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/S/

for Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

ANDA 74-726

MAR 6 1997

Upsher-Smith Laboratories, Inc.
Attention: Mark S. Robbins, Ph.D.
14905 23rd Avenue North
Minneapolis, MN 55447

Dear Sir:

Reference is made to your abbreviated new drug application dated August 8, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Klor-Con® M20 (Potassium Chloride Extended-release Tablets USP, 20 mEq).

Reference is also made to your correspondence dated April 4, 1996, and amendments dated June 20 and 26, 1996, July 2, 1996, and February 12, 1997.

We have completed the review of this abbreviated application and have concluded that, based upon the information you have presented to date, the drug is safe and effective for use as recommended in the submitted labeling. Therefore, the application is tentatively approved. This determination is based upon information available to the Agency at this time, which includes information in your application and the status of current good manufacturing practices of the facilities used in the manufacturing and testing of the drug products. Therefore, this determination is subject to change on the basis of new information that may come to our attention. This letter does not address notice issues related to the 180-day exclusivity provisions under section 505(j)(4)(B)(iv) of the Act.

The listed drug product referenced in your application is subject to period of patent protection which expires on September 5, 2006 (patent 4,863,743). However, you have informed us that litigation is underway in the United States District Court for the District of New Jersey, involving a challenge to patent 4,863,743 (Key Pharmaceuticals Inc., v. Upsher-Smith Laboratories Inc., Civil Action No. 95-6281 [WHW]). Therefore, final approval cannot be granted until:

1. a. the expiration of the 30-month period provided for in section 505(j)(4)(B)(iii) since the date of receipt of the 45-day notice required under section 505(j)(2)(B)(i), unless the court has extended or reduced the period because of the failure of either party to reasonably cooperate in expediting the action, or,

b. the date of court decision [505(j)(4)(B)(iii) (I), (II), or (III)], which has been interpreted by the Agency to mean the date of the final order or judgement of that court from which no appeal can be or has been taken, or,

c. the patent has expired, and

2. The Agency is assured there is no new information that would affect whether final approval should be granted.

Because the Agency is granting a tentative approval for this application, when you believe that your application may be considered for final approval, you must amend your application to notify the Agency whether circumstances have or have not arisen that may affect the effective date of final approval. Your amendment must provide:

1. a copy of a final order or judgement from which no appeal may be taken (which might not be the one from the district court), or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information, and

2. a. updated information related to labeling or chemistry, manufacturing and controls data, or any other change in the conditions outlined in this abbreviated application, or

b. a statement that no such changes have been made to the application since the date of tentative approval.

Any changes in the conditions outlined in this abbreviated application and the status of the manufacturing and testing facilities' compliance with current good manufacturing procedures are subject to Agency review before final approval of the application will be made.

In addition to, or instead of, the amendments referred to above, the Agency may, at any time prior to the final date of approval, request that you submit amendments containing the information requested above.

Failure to submit either or both amendments may result in rescission of this tentative approval determination, or delay in issuance of the final approval letter.

The drug product that is the subject of this abbreviated application may not be marketed without final Agency approval under Section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug before the effective final approval date is prohibited under Section 501 of

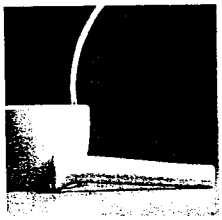
the Act. Also, until the Agency issues the final approval letter, these drug products will not be listed in the Agency's "Approved Drug Products with Therapeutic Equivalence Evaluations" list.

The amendment should be designated as a MINOR AMENDMENT in your cover letter. Before you submit the amendment, please contact James Wilson, Project Manager, at (301) 594-0310, for further instructions.

Sincerely yours,

/S/

Douglas L. Sporn
Director, Office of Generic Drugs
Center for Drug Evaluation and Research



Upsher-Smith Laboratories, Inc.

Innovative Pharmaceuticals Since 1919

February 12, 1997

VIA FACSIMILE (301) 594-0181

TA letter

Dr. Rabindra Patnaik
Acting Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
HFD-650, Room E-130
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

Dear Dr. Patnaik:

RE: Telephone Amendment #008 to ANDA #74-726
Klor-Con® M20 (Potassium Chloride Extended-release Tablets, USP, 20 mEq)
Additional Half-Tablet Comparative Dissolution and Content Uniformity Data

Reference is made to Upsher-Smith Laboratories, Inc. pending ANDA #74-726 for the above reference drug product.

Reference is also made to January 30, 1997 phone communications with Ms. Lizzie Sanchez, Consumer Safety Officer, Division of Bioequivalence, during which, additional comparative half-tablet dissolution and content uniformity data were requested.

Pursuant to this request, submitted herewith are the half-tablet comparative dissolution and content uniformity data between Klor-Con® M20 and the reference product, K-DUR® 20. As requested, this testing was conducted using the same lot of both Klor-Con® M20 (lot #15112) and K-DUR® 20 (lot #93772) as was used in the *in vivo* bioequivalence study and tested per Upsher-Smith's submitted finished product dissolution and assay methods.

UPSHER-SMITH

14905 23rd Avenue North Minneapolis, MN USA 55447-4709
Corporate Headquarters 612-473-4412 FAX# 612-476-4026 Sales & Distribution 1-800-654-2299

Upsher-Smith is presently scheduled to appear before the District Court on our motion for a summary judgment of non-infringement on March 10, 1997. Therefore, an expedited review of these data in support of a tentative approval letter for ANDA #74-726 by that date would be greatly appreciated.

This Amendment is being FAX'ed directly to the attention of Ms. Lizzie Sanchez. A hard copy is being submitted in duplicate for incorporation into our file.

Should you have any questions regarding these data or require additional information, please contact Dianne Gibbs, Regulatory Affairs Specialist at (612) 449-7261.

Sincerely,

UPSHER-SMITH LABORATORIES, INC.

Mark B. Halvorsen, Pharm.D.
Manager
Clinical and Regulatory Affairs

MBH/bac

Enclosure

COVINGTON & BURLING
1201 PENNSYLVANIA AVENUE, N. W.
P.O. BOX 7566
WASHINGTON, D.C. 20044-7566
(202) 662-6000

TELEFAX: (202) 662-6291
TELEX: 89-593 (COVLING WSH)
CABLE: COVLING

LECONFIELD HOUSE
CURZON STREET
LONDON W1Y 8AS
ENGLAND
TELEPHONE: 44-171-495-5655
TELEFAX: 44-171-495-3101

BRUSSELS CORRESPONDENT OFFICE
44 AVENUE DES ARTS
BRUSSELS 1040 BELGIUM
TELEPHONE: 32-2-512-9890
TELEFAX: 32-2-502-1598

THOMAS W. KRAUSE
DIRECT DIAL NUMBER
(202) 662-5297

December 18, 1995

BY HAND

Food & Drug Administration
Office of Generic Drugs
(HFD-600)
Metro Park North 2
7500 Standish Place
Rockville, MD 20855

NEW CORRES

Re: ANDA #74-726: Notice of Patent Infringement Lawsuit Filed Within 45 days of Notice to NDA Holder

Dear Sir or Madam:

Pursuant to 21 CFR § 314.107(f)(2), I am writing to notify you that a patent infringement action has been brought in the United States District Court for the District of New Jersey as follows:

(i) The action concerns ANDA #74-726;

(ii) The name of the abbreviated new drug applicant is Upsher-Smith Laboratories, Inc.; and

(iii) The name of the drug product for which Upsher-Smith seeks approval under ANDA #74-726 is KLOR-CON® M, (20 mEq potassium chloride extended-release tablets, USP).

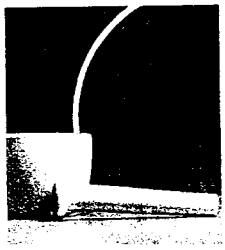
(iv) Upsher-Smith Laboratories sent notice of its ANDA #74-726 to Key Pharmaceuticals, Inc., on November 3, 1995. Key Pharmaceuticals, Inc. received notice of Upsher-Smith's ANDA #74-726 on or about November 7, 1995. I hereby certify that the patent infringement action concerning ANDA #74-726 is captioned Key Pharmaceuticals, Inc. v. Upsher-Smith Laboratories, Inc., Civ. Action No. 95-6281 (WHW) and was filed in the United States District Court for the District of New Jersey on December 15, 1995, less than 45 days after Key Pharmaceuticals received notice of ANDA #74-726. A copy of the complaint is enclosed.

RECEIVED
DEC 19 1995
GENERIC DRUGS

Sincerely yours,

Thomas W. Krause
Attorney for
Key Pharmaceuticals, Inc.

Enclosure
cc: Mr. Donald Hare



Upsher-Smith Laboratories, Inc.

Innovative Pharmaceuticals Since 1919

September 24, 1998

CERTIFIED MAIL / RETURN RECEIPT REQUESTED

Douglas L. Sporn
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place
HFD-600
Rockville, MD 20855-2773

NDA ORIG AMENDMENT
AM

RE: ANDA 74-726; Klor-Con® M20 (Potassium Chloride Extended-release Tablets, USP, 20mEq)
Minor FAX Amendment # 013: Response to September 10 teleconference concerning final dissolution specifications and stability testing

Dear Mr. Sporn:

Reference is made to our pending Abbreviated New Drug Application, 74-726, for Klor-Con® M20 (Potassium Chloride Extended-release Tablets, USP, 20mEq). Reference is also made to the two previous written communications provided by Upsher-Smith to the Agency on August 20th and September 2nd.

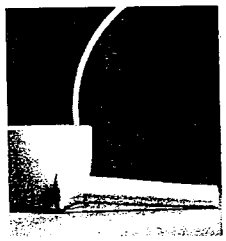
In a telephone conversation on September 10, 1998, Mark Anderson, the Project Manager for ANDA 74-726, requested that Upsher-Smith incorporate the final release dissolution specifications, agreed to in our August 20th correspondence, into the stability testing program. The dissolution specifications discussed are as follows:

1 hour	NLT	%	and	NMT	%
2 hours	NLT	%	and	NMT	%
6 hours	NLT	%	and	NMT	%
12 hours	NLT	%			

RECEIVED
SEP 29 1998
GENERIC DRUGS

UPSHER-SMITH

14905 23rd Avenue North Minneapolis, MN USA 55447-4709
Corporate Headquarters 612-473-4412 FAX= 612-476-4026 Sales & Distribution 1-800-654-2299



Upsher-Smith Laboratories, Inc.

Innovative Pharmaceuticals Since 1919

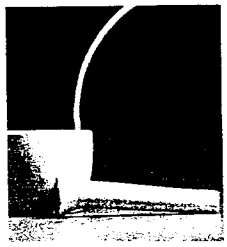
Upsher-Smith Laboratories, Inc. agrees to make the modifications to the release specifications as well as the stability program as recommended by the Agency during the September 10th teleconference. Therefore, Upsher-Smith is amending the application to include the following:

- **Attachment I** provides the necessary revisions to the corresponding page from section *XV. Controls for Finished Dosage Form* of the CMC (pg. 4577). This page lists the current methods and new specifications as agreed upon.
- **Attachment II** provides the necessary revisions to the corresponding page from section *XVII. Stability* of the CMC (page 4879). Due to revisions, page number 4879 now expands to a second page (page 4879a). This page contains the revised description of the dissolution testing and the revised testing schedule.
- **Attachment III** provides the finished product specifications, incorporating the agreed upon dissolution specifications.
- **Attachment IV** contains the revised controlled room temperature stability data for the original bioequivalence lot in the intended marketing containers.

This Amendment (# 013) is being submitted via facsimile, as directed by Mark Anderson. A hard copy of this Amendment is also being submitted in duplicate for incorporation into our file. Please note that all references to Klor-Con® M10 (Potassium Chloride Extended-release Tablets, USP. mEq) have been removed per Amendment # 002 submitted to the Agency on October 12, 1995.

In addition, Upsher Smith certifies that no changes, other than those noted above, have been made to the labeling or Chemistry, Manufacturing and Controls data or any other part of the application that would affect approval since the date of the tentative approval.

It is our understanding this Amendment concludes the responses to any remaining questions, therefore Upsher-Smith Laboratories, Inc. anticipates approval with 180 days of marketing exclusivity from the date of first commercial introduction.



Upsher-Smith Laboratories, Inc.

Innovative Pharmaceuticals Since 1919

As required per 21 CFR 314.94(d)(5), we hereby certify that a field copy of this Amendment (#013) has been submitted to the Minneapolis District FDA for their information. Should you have any questions regarding this Amendment or require additional information, please contact Michael Poirier, Regulatory Affairs Specialist at (612) 449-7261.

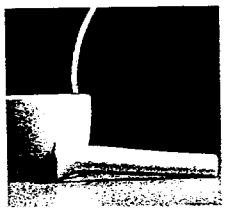
Sincerely,
UPSHER-SMITH LABORATORIES, INC.

Mark B. Halvorsen, Pharm D.
Manager, Clinical and Regulatory Affairs

enclosure

cc:

Mark Anderson
Project Manager
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
HFD-617
Rockville, MD 20855-2773



Upsher-Smith Laboratories, Inc.

Innovative Pharmaceuticals Since 1919

September 2, 1998

NEW CORRESP

NC to Fax

CERTIFIED MAIL / RETURN RECEIPT REQUESTED

Douglas L. Sporn
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place
HFD-600
Rockville, MD 20855-2773

RE: ANDA 74-726; Klor-Con® M20 (Potassium Chloride Extended-release Tablets, USP, 20mEq)
Minor FAX Amendment # 012: Response to the Tentative Approval Letter on March 6, 1997

Dear Mr. Sporn:

Reference is made to our pending Abbreviated New Drug Application, 74-726, for Klor-Con® M20 (Potassium Chloride Extended-release Tablets, USP, 20mEq). In a telephone conversation on August 28, 1998, Mark Anderson, the Project Manager for ANDA 74-726, requested that Upsher-Smith formally respond to the tentative approval letter dated March 6, 1997.

In that letter, the Agency requested Upsher-Smith to amend the application by submitting notification regarding any changes that may affect the effective date of final approval. The Agency asked that the Amendment provide:

1. a. **a copy of a final order or judgment from which no appeal may be taken (which might not be the one from the district court), or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information, and**

In response, Upsher-Smith asks the Agency to refer to our correspondence concerning the notification of final court action dated February 13, 1998 (Amendment # 010).

2. a. **updated information related to the labeling or chemistry, manufacturing and controls data, or any other change in the conditions outlined in this abbreviated application, or**

   b. **a statement that no such changes have been made to the application since the date of tentative approval.**

In response to 2a. and 2b., Upsher Smith hereby certifies that no changes have been made to the labeling or Chemistry, Manufacturing and Controls data or any other part of the application that would affect approval since the date of the tentative approval.

Finally, Upsher-Smith asks the Agency to refer to the correspondence dated August 20, 1998 in which Upsher-Smith agreed to the final dissolution specifications posed by the Agency. In addition, the Amendment provided both final product specifications and controlled room temperature stability data for the original bioequivalence lot in the intended marketing containers.

It is our understanding this Amendment concludes the responses to any remaining questions, therefore Upsher-Smith Laboratories, Inc. anticipates approval with 180 days of marketing exclusivity from the date of first commercial introduction.

As required per 21 CFR 314.94(d)(5), we hereby certify that a field copy of this Amendment (#012) is being submitted to the Minneapolis District FDA for their information. Should you have any questions regarding this Amendment or require additional information, please contact Michael Poirier, Regulatory Affairs Specialist at (612) 449-7261.

Sincerely,

UPSHER-SMITH LABORATORIES, INC.

Mark B. Halvorsen, Pharm D.
Manager, Clinical and Regulatory Affairs

cc:

Mark Anderson
Project Manager
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place
HFD-617
Rockville, MD 20855-2773

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on last page.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT: Upsher-Smith Laboratories, Inc.

DATE OF SUBMISSION: September 2, 1998

TELEPHONE NO. *(Include Area Code)*: (612) 473-4412

FACSIMILE (FAX) Number *(Include Area Code)*: (612) 476-4026

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*:
4905 23rd Avenue North
Minneapolis, MN 55447

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE: N/A

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued): 74-726-A-012

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*: Potassium Chloride Extended-release Tablets, USP

PROPRIETARY NAME *(trade name)* IF ANY: Klor-Con® M20

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*: Potassium Chloride

CODE NAME *(If any)*: N/A

DOSAGE FORM: Tablet

STRENGTHS: 20 mEq

ROUTE OF ADMINISTRATION: Oral

(PROPOSED) INDICATION(S) FOR USE:
Potassium Supplementation

APPLICATION INFORMATION

APPLICATION TYPE (Check one)
☐ NEW DRUG APPLICATION (21 CFR 314.50)
☒ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

FOR AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

FOR AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug: K-DUR® Tablets
Holder of Approved Application: Schering

TYPE OF SUBMISSION (Check one)
☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ 8(U)PAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION
Fax amendment: Response to tentative approval letter

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED: 1

THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

N/A

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

N/A

This application contains the following items: *(Check all that apply)*

	1. Index
	2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k)(1))
X	17. Field copy certification (21 CFR 314.5 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
	19. OTHER (Specify) Tentative Approval Letter Certification Statement

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80,314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

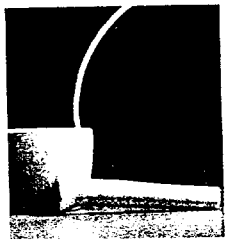
If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
	Mark B. Halvorsen, Pharm.D. Mgr., Clinical & Regulatory Affairs	9/2/98

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
14905 23rd Avenue North Minneapolis, MN 55447	(612) 473-4412



Upsher-Smith Laboratories, Inc.

Innovative Pharmaceuticals Since 1919

August 20, 1998

BY FACSIMILE AND FEDERAL EXPRESS

NEW CORRESP

(N/AB)

Douglas L. Sporn
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place
HFD-600
Rockville, MD 20855-2773

RE: ANDA 74-726; Klor-Con® M20 (Potassium Chloride Extended-release Tablets, USP, 20mEq)
Minor FAX Amendment # 011: Finished product dissolution specifications.

Dear Mr. Sporn:

Reference is made to our pending Abbreviated New Drug Application, 74-726, for Klor-Con® M20 (Potassium Chloride Extended-release Tablets, USP, 20mEq). Reference is also made to our correspondence concerning the notification of final court action on February 13, 1998 (Amendment #010).

In a letter from Dr. Rabindra Patnaik, dated March 3, 1997, the Agency recommended the following release specifications for dissolution:

1 hour				NMT	%
2 hours	NLT	%	and	NMT	%
6 hours	NLT	%	and	NMT	%
12 hours	NLT	%			

RECEIVED

AUG 24 1998

GENERIC DRUGS

UPSHER-SMITH

14905 23rd Avenue North Minneapolis, MN USA 55447-4709
Corporate Headquarters 612-473-4412 FAX# 612-476-4026 Sales & Distribution 1-800-654-2299

Based on this request, Upsher-Smith Laboratories, Inc. filed Amendment # 009 on November 7, 1997 requesting reevaluation of the one hour *in vitro* dissolution specification. The data filed in that amendment supported the use of the following one hour dissolution specification:

1 hour	NMT	%

Following Amendment # 009, a Fax was received from the Agency on June 18, 1998. The Fax included a memorandum from the Division of Bioequivalence which recommended, based on the evaluation of Amendment # 009, the following finished product dissolution specifications:

1 hour	NLT	%	and	NMT	%
2 hours	NLT	%	and	NMT	%
6 hours	NLT	%	and	NMT	%
12 hours	NLT	%			

Upsher-Smith Laboratories, Inc. agrees to make the modifications to the release specifications as recommended by the Division of Bioequivalence. Attachment I provides the revisions to the corresponding page from section *XV. Controls for Finished Dosage Form* of the CMC (pg. 4576). This page lists the current methods and new specifications as agreed upon. Please note these specifications are for release testing only and that the routine stability testing will remain as listed in our current application.

Also included in this amendment are the finished product specifications and the updated controlled room temperature stability data for the original bioequivalence lot in the intended marketing containers.

This Amendment (# 011) is being submitted via facsimile, as directed by the Agency's facsimile deficiency cover letter. A hard copy if this Amendment is also being submitted in duplicate for incorporation into our file.

It is our understanding this Amendment concludes the responses to all deficiency questions, therefore Upsher-Smith Laboratories, Inc. anticipates a timely approval.

As required per 21 CFR 314.94(d)(5), we hereby certify that a field copy of this Amendment (#011) is being submitted to the Minneapolis District FDA for their information. Should you have any questions regarding this Amendment or require additional information, please contact Michael Poirier, Regulatory Affairs Specialist at (612) 449-7261.

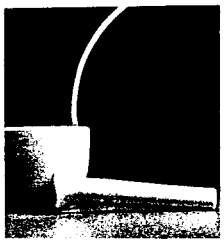
Sincerely,

UPSHER-SMITH LABORATORIES, INC.

Mark B. Halvorsen, Pharm D.
Manager, Clinical and Regulatory Affairs

Enclosure

cc: Mark Anderson
Project Manager
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place
HFD-617
Rockville, MD 20855-2773



NAI
2/27/98

Upsher-Smith Laboratories, Inc.

Innovative Pharmaceuticals Since 1919

February 13, 1998

CERTIFIED MAIL/RETURN RECEIPT REQUESTED

NEW CORRESP

NC

Douglas L. Sporn
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place
Room 286, HFD-600
Rockville, MD 20855-2773

RE:
ANDA 74-726; Klor-Con® M20 (Potassium Chloride Extended-release Tablets, USP, 20 mEq)
Amendment #010 Providing FDA Notification of Final Court Action

Dear Mr. Sporn:

Reference is made to our pending Abbreviated New Drug Application, 74-726, for the above referenced drug product.

As required per 21 CFR 314.107(e), enclosed please find a copy of the Stipulation Of Dismissal for purposes of notifying FDA of a court settlement regarding the patent litigation involving the above referenced drug product. Given the settlement of this case and assuming successful resolution of any pending technical issues, ANDA 74-726 can be approved immediately.

This Amendment #010 is being submitted in duplicate for incorporation into our file.

If there are any questions concerning this submission, please contact me at (612) 449-7267.

Sincerely,

UPSHER-SMITH LABORATORIES, INC.

Cynthia G. Farner

Cynthia G. Farner
Sr. Regulatory Affairs Specialist

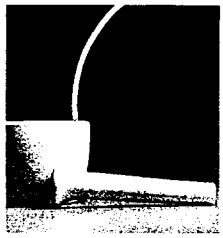
RECEIVED
FEB 20 1998
GENERIC DRUGS

2-20-98

UPSHER-SMITH
14905 23rd Avenue North Minneapolis, MN 55447
Telephone 612-473-4412 Telex# 6502644714 FAX# 612-476-4026

enclosure

cc: Donald B. Hare
Special Assistant, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place
Room 286, HFD-604
Rockville, MD 20855-2773



Upsher-Smith Laboratories, Inc.

Innovative Pharmaceuticals Since 1919

November 7, 1997

FEDERAL EXPRESS

Rabindra Patnaik, Ph.D.
Acting Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Dr. Patnaik:

RE: ***ANDA #74-726; Klor-Con® M20 (Potassium Chloride Extended-release Tablets, USP), 20 mEq***
Amendment #009 to Request Reevaluation of the One Hour In Vitro Dissolution Specification

Reference is made to ANDA 74-726, originally submitted August 8, 1995 for Klor-Con® M20 (Potassium Chloride Extended-release Tablets, USP), 20 mEq, and tentatively approved on March 6, 1997.

Reference is also made to the Division of Bioequivalence letter dated September 6, 1996 stating that the Division had completed its review of ANDA 74-726, and had no further comments at that time. A copy of the September 6, 1996 letter is included as Attachment #1. In this communication, the Division provided the *in vitro* dissolution specifications which included a one hour specification of NMT %, the same as that proposed by Upsher-Smith in the original application.

Reference is also made to the Division of Bioequivalence letter dated March 3, 1997, again stating that the Division had completed its review of ANDA 74-726, and had no further comments at that time. A copy of the March 3, 1997 letter is included as

Attachment #2. This second letter was prompted by the review of additional half-tablet dissolution data which was submitted subsequent to the Agency's January 30, 1997 request. In the Division's March 3, 1997 letter, *in vitro* dissolution specifications were again provided, however the one hour dissolution specification was revised without comment to NMT %.

This Amendment is to request that the Agency reevaluate the one hour dissolution specification based on additional one hour dissolution data provided herewith.

Upon receipt of the Division's March 3, 1997 letter, Upsher-Smith has reevaluated the previously submitted one hour dissolution data for twelve tablets of the Klor-Con® M20 bioequivalence study lot (Lot #15112) as well as six tablet dissolutions from each of nine additional trial lots, all formulated and manufactured equivalently to the biolot. A summary of these additional dissolution data as well as the frequency distribution of the data are provided below. Individual tablet data are included as Attachment #3.

Klor-Con® M20 One Hour Dissolution Results Summary
Apparatus: Paddles @ 50 rpm n=10 lots

Statistic	% Released
Max + 2SD	
Max + SD	
M20 Max	
M20 Avg	
M20 Min	
Min – SD	
Min – 2SD	

Frequency Distribution Table:

% Dissolved	# of Tablets
%	0
%	0
%	0
%	8
%	27
%	29
%	2
%	0
%	0

Evaluation of these data demonstrate slight lot to lot variability, as evidenced by a maximum one hour dissolution value of % and a minimum value of %. Contributing to this variability is the USP assay method which specifies quantitation by atomic absorption, a more variable method than many other laboratory techniques. However, based on reevaluation of the available dissolution data, Upsher-Smith proposes a one hour specification of NMT %, as opposed to NMT %, as was originally submitted. The specification of NMT %, based on two standard deviations above the high value obtained from the biolot and nine additional, equivalent trial lots, is reasonable, provides an effective process control measure, and establishes a specification based on the capabilities of the manufacturing process.

Furthermore, a specification of NMT % at one hour is consistent with the USP 2-hour dissolution specification for Potassium Chloride Extended-release Tablets. The USP specification for release at 2 hours is Q %. The monograph also provides an acceptance table which states, "Each unit is within the range Q %." Therefore, individual tablets must meet the specification of % at 2 hours. The Klor-Con® M20 one hour dissolution specification is not based on a Q value, but instead incorporates the range of % for individual tablets. In evaluating individual tablet data, Acceptance Table 1 from USP Drug Release Chapter <724> is applied. Therefore, Upsher-Smith's proposed one hour specification of NMT % is not in conflict with the USP 2-hour specification of %.

In conclusion, Upsher-Smith requests that the Agency evaluate the dissolution data provided and grant approval of the one hour *in vitro* dissolution specification of NMT %. The *in vitro* dissolution specifications at the 2, 6, and 12 hour timepoints remain as currently approved.

This Amendment #009 is being submitted in duplicate for incorporation into our file.

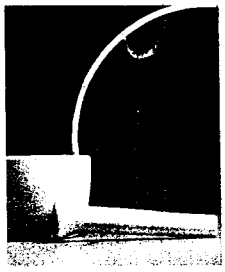
Should you have any questions regarding these data or require additional information, please contact Dianne Gibbs, Regulatory Affairs Specialist at (612)449-7261.

Sincerely,

UPSHER-SMITH LABORATORIES, INC.

Mark B. Halvorsen, Pharm.D.
Manager
Clinical and Regulatory Affairs

enclosures



Upsher-Smith Laboratories, Inc.
Innovative Pharmaceuticals Since 1919

NOTED 4/2/97
NEW CORRESP
FORWARDED TO LARRY GALVIN

BIOAVAILABILITY

March 24, 1997

CERTIFIED MAIL/RETURN RECEIPT REQUESTED

Nai 3/28/97

Nicholas Fleisher, Ph.D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
HFD-650, Room E-130
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

RECEIVED
MAR 27 1997
GENERIC DRUGS

Dear Dr. Fleisher:

RE: ANDA 74-726; Klor-Con® M20 (Potassium Chloride Extended-release Tablets, USP), 20 mEq

Reference is made to ANDA 74-726, originally submitted August 8, 1995, and tentatively approved on March 6, 1997.

Reference is also made to the Division of Bioequivalence's March 3, 1997, letter which states the following two comments regarding the review of the above referenced ANDA: 1) The Division has completed its review of the ANDA and has no further questions at this time; and 2) The *in vitro* test results on half tablets (submitted February 12, 1997) are acceptable, and that dissolution testing should be incorporated into the firm's manufacturing controls and stability programs. The letter then went on to state the dissolution parameters and specifications, as submitted in the ANDA.

Reference is also made to my March 13, 1997, phone communication with Mr. Larry Galvin, Consumer Safety Officer, Division of Bioequivalence, during which I referenced the March 3, 1997 letter and asked for clarification on what seemed to be a requirement to incorporate half-tablet dissolution testing into the manufacturing controls and stability testing for Klor-Con® M20. I explained that whole tablet dissolution was already included in the manufacturing controls and stability testing, and that the addition of half-tablet dissolution was inappropriate. Furthermore, half-tablet dissolution data had only been submitted upon the Agency's request as additional information in support of tentative approval of the application. Mr. Galvin agreed that the wording of the letter seemed in error and after checking, informed me that the letter was "poorly worded." He stated that only whole tablet dissolution, as previously committed to, need be incorporated into the manufacturing controls and stability testing for Klor-Con® M20, and not half-tablet dissolutions.

Since the March 3, 1997 letter seemed to be in error, I asked Mr. Galvin if the Division would be issuing a second corrected letter. Mr. Galvin stated that a second letter would not be issued but that he would document our phone conversation and incorporate it into the ANDA file.

This letter formally provides documentation of the above referenced March 13, 1997, phone communication which clarified the Division of Bioequivalence's March 3, 1997 letter. The letter should have indicated that; 1) review of the ANDA is complete; and 2) The half-tablet *in vitro* dissolutions data are acceptable, and that whole tablet dissolution (as previously committed to) should be part of the manufacturing controls and stability testing of the product.

The letter is being submitted in duplicate for incorporation into our file. Should you have any questions, please contact me at (612) 449-7261.

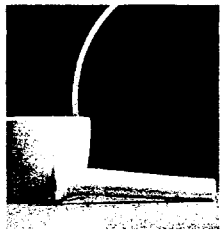
Sincerely,

UPSHER-SMITH LABORATORIES, INC.

Dianne Gibbs

Dianne Gibbs
Regulatory Affairs Specialist

DG/bac



Upsher-Smith Laboratories, Inc.

Innovative Pharmaceuticals Since 1919

March 14, 1997

CERTIFIED MAIL/RETURN RECEIPT REQUESTED

Nicholas Fleischer, Ph.D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
HFD-650, Room E-130
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

Dear Dr. Fleischer:

RE: ANDA 74-726; Klor-Con® M (Potassium Chloride Extended-release Tablets, USP) Request for Clarification of Agency's Refusal to File mEq Tablet Based on Request for Waiver of *In vivo* Bioequivalence

Reference is made to ANDA 74-726, originally submitted August 8, 1995 for Klor-Con® M (Potassium Chloride Extended-release Tablets, USP) 20 mEq.

This communication is to request clarification of the Agency's policy regarding granting requests for waiver of *in vivo* bioequivalence for a lower strength, controlled-release tablet (i.e., mEq) when an *in vivo* bioequivalence study has been performed on the dosage proportional, higher strength tablet (i.e., 20 mEq).

Upsher-Smith Laboratories, Inc. originally submitted ANDA 74-726 for Klor-Con® M (Potassium Chloride Extended-release Tablets) 20 mEq tablet strengths. An *in vivo* bioequivalence study with the 20 mEq tablet was submitted along with a request for waiver of *in-vivo* bioequivalence for the 10 mEq tablet strength. The request for waiver of *in vivo* bioequivalence for the mEq tablet was based on the tablets being dosage proportional and comparative *in vitro* dissolution studies. The Agency refused to file the original ANDA based on the request for waiver of *in vivo* bioequivalence for the mEq strength.

Recently, Upsher-Smith Laboratories, Inc. has been made aware by various sources that the Office of Generic Drugs may have granted other requests for waiver of *in vivo* bioequivalence for Potassium Chloride Extended-release mEq Tablets. These waivers were supposedly granted based on dosage proportionality, comparative *in vitro* dissolution and an *in vivo* bioequivalence study using the 20 mEq tablet strength, the same information included in the original ANDA 74-726.

Should these other waivers have been granted, Upsher-Smith would be placed at an extreme competitive disadvantage. Upsher-Smith is a small generic pharmaceutical company and the cost to conduct an additional *in vivo* bioequivalence study, not to mention the delay it causes in approval of a mEq tablet strength, is of great impact. Upsher-Smith, therefore, requests that the Agency clarify whether or not these other rumored requests for waiver of *in vivo* bioequivalence for Potassium Chloride Extended-release mEq Tablets have indeed been granted.

The following information is provided for your convenience in looking into this matter:

- Reference is made to the Agency's Refuse to File letter dated August 28, 1995, which gave two reasons for refusing to file. One of these reasons stated that although a bioequivalence study for the 20 mEq strength had been submitted, an *in vivo* bioequivalence waiver could not be granted for the mEq strength under 21 CFR 320.22(d)(2)(iv) which excluded controlled release dosage forms from the *in vivo* waiver request provision. (The *in vivo* waiver submitted had been based on dosage proportionality of the mEq tablet to the 20 mEq tablet strength and comparative *in vitro* dissolution data.)

- Reference is made to Amendment 001 to ANDA 74-726 dated September 11, 1995, in which Upsher-Smith acknowledged the Agency's comment regarding the unacceptability of the *in vivo* bioequivalence waiver for the mEq strength but noted that the innovator product, K-DUR® 10 mEq Tablet, was granted approval based on dosage proportionality alone. Clinical studies had been performed on the K-DUR® 20 mEq tablet only. No clinical studies or bioavailability studies had been conducted by the innovator on K-DUR® mEq tablets. For this reason, Upsher-Smith requested a full review of the request for waiver by the Division of Bioequivalence.

- Reference is made to the Agency's Refuse to File letter dated October 3, 1995, which acknowledged our comments regarding request for waiver of *in vivo* bioequivalence for the mEq strength but again stated that the application could not be filed per 21 CFR 320.22(d)(2)(iv) and current policy of the Division of Bioequivalence which required *in vivo* bioequivalence studies on each strength of a controlled-release tablet.

- Reference is made to Amendment 002 to ANDA 74-726 dated October 12, 1995, in which Upsher-Smith withdrew the Klor-Con® M10 tablet formulation mEq tablet strength) from the ANDA.

- Reference is made to the Agency's October 30, 1995 acknowledgment/filing notice listing October 13, 1995 as the date the application was acceptable for filing.

- Reference is finally made to a May 9, 1996 phone communication with Mr. Larry Galvin, CSO, Division of Bioequivalence. During this communication, Mr. Galvin stated that the bioequivalence review of the ANDA was complete and the Agency had some comments on the mEq strength. At that point, it was explained that pursuant to two Refuse to File letters, the mEq strength had been withdrawn. Mr. Galvin stated that this information had not been relayed to the reviewer and the review would now need to be rewritten.

The fact that the Division of Bioequivalence reviewed the request for waiver and commented on the mEq tablet data, as originally submitted, leads one to believe that the Agency had found the request for waiver to be acceptable. Therefore, should the Agency find that other similar requests for waiver have indeed been granted, Upsher-Smith asks that the request for waiver of *in vivo* bioequivalence for the Klor-Con® M10, mEq tablet strength, also be reviewed by the Agency in support of approval of this tablet strength. Moreover, even if the Agency finds that other such requests for waiver have not been granted, Upsher-Smith asks that the Agency now agree to review our request for waiver of *in vivo* bioequivalence for the Klor-Con® M10 or commence proceedings to withdraw approval of K-DUR® 10.

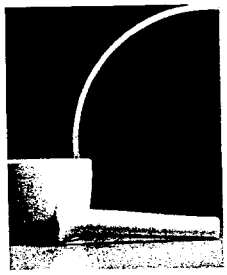
Should you have any questions or require additional information, please contact Dianne Gibbs, Regulatory Affairs Specialist at (612) 449-7261. This communication is being submitted in duplicate for incorporation into our file.

We appreciate your taking the time in looking into this matter. We hope you can understand Upsher-Smith's concern regarding the fair and equitable treatment of all companies within the pharmaceutical industry by the Agency.

Sincerely,

UPSHER-SMITH LABORATORIES, INC.

Mark B. Halvorsen, Pharm.D.
Manager
Clinical and Regulatory Affairs



ORIG AMENDMENT

Upsher-Smith Laboratories, Inc.

Innovative Pharmaceuticals Since 1919

July 2, 1996

CERTIFIED MAIL/RETURN RECEIPT REQUESTED

Rashmikant M. Patel, Ph.D.
Director, Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Dr. Patel:

RE: ANDA 74-726 - Klor-Con® M20 (Potassium Chloride Extended-release Tablets, USP 20 mEq)
Major Amendment #007 to Provide Response to the Agency's March 27, 1996 Deficiency Letter

Reference is made to our pending Abbreviated New Drug Application #74-726 for the above referenced drug product.

In response to the Agency's deficiency letter of March 27, 1996, an amendment is submitted herewith to the above referenced ANDA.

This amendment has been designated as "major" by the Agency. Each deficiency item enumerated in the Agency's letter is shown in bold print and has been addressed in the sequence that it was presented.

A. Chemistry Deficiencies

1. **The DMF you referenced for the drug substance chemistry, manufacturing, and controls (CMC) information is a DMF. Please provide a letter of authorization for the DMF describing the manufacturing, purification, testing, and packaging procedures for the drug substance. Alternatively, this information may be submitted to the application by you.**

, the holder of the above referenced DMF for the drug substance, Chemistry, Manufacturing, and Controls (CMC) information has been in contact with Mr. Paul Chapman, Project Officer, FDA, regarding their DMF. During this communication, it was explained that DMF contains all information, as appropriate, pertaining to the Chemistry, Manufacturing, and Controls of Potassium Chloride, USP. Therefore, per Mr. Chapman, DMF was converted from a DMF. A copy of a letter from to Upsher-Smith Laboratories, Inc. documenting their communications with Mr. Chapman and the conversion of their DMF to a DMF is included as Attachment #1.

2. **No information is provided in reference to the corrugated shipping container used for the bulk package of tablets. Please respond to the following:**

   a. **Please provide information regarding the materials of construction and regulatory status for the components of the corrugated shipping container.**

   b. **Please provide test data indicating the container closure system provides an adequate barrier for this product. Specifically, the container must meet the permeability and resealability requirements for tight containers.**

   c. **Please provide information regarding the resealing procedures for this container. Please be informed that twist ties are generally not considered to be adequate for reproducible resealing.**

   d. **Please provide information regarding the intended purpose for these containers. If they are to be shipped to a repackager, we require evidence of an agreement to use appropriate market packaging materials.**

   Pursuant to the above comments regarding the Klor-Con® M20 bulk pack of tablets, Upsher-Smith Laboratories, Inc. hereby withdraws this package size from the ANDA. Klor-Con® M20 tablets will only be packaged in bottles of 100, 500, and 1000 tablets and unit dose cartons of 100 tablets. The revised final printed package insert provided herewith (see Attachment #6) reflects the deletion of the bulk pack of tablets.

3. **In reference to the coated granule release specifications, please respond to the following:**

   a. **The dissolution specification is much wider than the data you provided from 38 different granulation production batches. Please revise the specification to more closely characterize the manufactured material.**

   In the original ANDA, Upsher-Smith Laboratories, Inc. proposed a dissolution specification for the coated KCl granules of NLT % and NMT % KCl released at 2 hours. This specification was based on data obtained from 38 different granulation production batches. Among these 38 granulation lots were the composite granulations for Klor-Con® M10 lot #60154, and Klor-Con® M20 lot #15112. These Klor-Con® M10 and the Klor-Con® M20 granulation 2-hour dissolution values represent a composite of 6 individual granulation lots each. The individual 2-hour dissolution values for each of these granulation lots are also included among the 38 lots evaluated. Therefore, only data from the 36 individual granulation production lots are appropriate for reconsidering this specification.

   Upsher-Smith Laboratories, Inc. re-evaluated the individual sample 2-hour dissolution results for the 36 granulation lots manufactured (162 observations total). Individual sample data in tabular form, a graphic representation of the data point distribution, as well as a frequency table of the dissolution results are included as Attachment #2. Based on the minimum 2-hour dissolution value obtained of %, less the standard deviation of %, and the maximum dissolution value obtained of %, plus the standard deviation of %, the dissolution specification for the coated granules has been tightened to NLT % and NMT % to more closely reflect the results obtained for the manufactured material. A revised Coated Potassium Chloride Granules raw material specification sheet which incorporates the tightened 2-hour Dissolution Specification is included as part of Attachment #2 as well.

   b. **Please perform the methanol residue test as a routine in-process control with a limit specification characteristic of the data provided (about 50 ppm). Once enough data is available for post approval batches, a supplement may be provided to discontinue this test.**

   Upsher-Smith Laboratories, Inc. commits to perform the methanol residual test as a routine in-process control for every lot of granules received from The specification for methanol residuals will be revised from NMT ppm to NMT ppm. A revised granules specification sheet which incorporates the methanol residual test is included with Attachment #2. Furthermore, this testing will now be performed in-house. A copy of the test method MD-045-00 "Determination of Methanol in Coated Potassium Chloride Granules", along with the test method validation protocol and report, are included as Attachment #3. Method MD-045-00, upon being transferred into the Quality Services laboratory, will be assigned method #QS-271-00. The revised granules specification sheet provided, references Method QS-271 for performing the methanol residual test.

d. **The post approval stability commitment indicates that % of the production batches will be tested annually while on stability. Upsher-Smith Laboratories, Inc. should commit to place at least one batch on stability each year and to test them at 0, 3, 6, 9, 12, 18, and 24 months.**

Upsher-Smith Laboratories, Inc. hereby commits to place at least one batch of Klor-Con® M20 tablets, or at least 1% of all Klor-Con® M20 production batches manufactured annually, whichever is greater, on stability each year and to test them at 0, 3, 6, 9, 12, 18, and 24 months. A revised stability commitment is included as Attachment #4.

5. **The particle size specification for the Potassium Chloride USP raw material is too broad. The amount retained on the screen is specified as NLT %. The data indicate that the biobatch was manufactured with a batch that had % retained on the screen. Please revise the screen specification to more closely match the material that was used in the biobatch.**

Based on intra-laboratory testing that involved Upsher-Smith Laboratories, Inc. , a revised particle size specification for the amount retained on the screen has been developed. To perform these particle size analyses, Upsher-Smith Laboratories, Inc. developed a new particle size test method which uses equipment and screens. The test method, is included in Attachment #5. This method provides more accurate and reproducible particle size results when testing Potassium Chloride, USP raw material, than the test method submitted in the original ANDA. All of the samples were tested in triplicate in order to determine the normal variation in testing. Particle size test results obtained for Potassium Chloride mesh, USP, lots #K4150 and #K4173 (used in the manufacture of Klor-Con® M20 Lot #15112 and Klor-Con® M10 Lot #60154, respectively), using the method, as well as the particle size data obtained per the method, as submitted in the original ANDA, are included as Attachment #5. The particle size test result for Lot #K4150 (used in the manufacture of the biobatch), submitted in the original ANDA, using the method, was % retained on the mesh screen. This value is no longer applicable with respect to the development of the revised particle size specification due to the different test methods used.

Using the attached data, Upsher-Smith Laboratories, Inc., in cooperation with has established a specification for the mesh screen of % retained on the mesh screen. This range is based on 3 standard deviations from the mean of all results obtained. The specification for the mesh (retain % maximum) and the mesh (through % maximum) will remain the same. will perform a particle size analysis per Upsher-Smith method on all lots of Potassium Chloride mesh, USP they provide to us. Particle size results will be provided on the Certificate of Analysis for each lot received. An updated raw material specification sheet for Potassium Chloride mesh, USP, which incorporates this revised particle size specification, is included with Attachment #5.

B. Labeling Deficiencies

All labeling deficiencies enumerated in the Agency's letter have been corrected and the labeling revised accordingly.

Please Note:
Regarding comment B.3.e.i., which pertains to wording in the Dosage and Administration section of the package insert, Upsher-Smith Laboratories, Inc. contacted Dr. White, Labeling Reviewer, Office of Generic Drugs for clarification. Per Dr. White, rather than revising Paragraph 3 of the Dosage and Administration section to read, "Each Klor-Con® M20 extended-release tablet provides 1500 mg of potassium chloride and 20 mEq potassium," this statement was revised to read, "Each Klor-Con® M20 extended-release tablet provides 1500 mg of potassium chloride equivalent to 20 mEq potassium."

Also, the packaging code "245-58" has been added to the top of each unit dose blister.

Labeling comparisons, as well as examples of final printed labeling are included herewith as Attachment #6. Twelve additional sets of final printed labeling are included, separately bound, to accompany the archival copy of this amendment.

In addition to responding to the items enumerated in the Agency's deficiency letter, the following information is provided:

1. manufacturer of the in-process Klor-Con® M granules, has notified Upsher-Smith Laboratories, Inc. that they are in the process of revising their Drug Master File, DMF This was necessitated by the addition of a Research and Development suite, manufacturing areas, organizational changes and a change in their security system. A copy of this notification letter is included as Attachment #7.

2. manufacturer of the inactive ingredient, Ac-Di-Sol® croscarmellose sodium, NF, has notified us that they have updated their DMF to add an additional manufacturing site. A copy of this notification letter is included as Attachment #8.

3. The following Quality Services (QS) test methods and specifications have been revised and are included as Attachment #9:

   - QS test method QS-149-00, "Croscarmellose Sodium - ID Tests" was revised per USP 23 Supplement #3 to include Identification Test C - Precipitation Test. The new method number is QS-149-01.

   - QS test method QC-236-01 "Potassium Chloride Raw Material Test Method", under the procedure for the Acidity or Alkalinity Identification, was revised to read, ' N Sodium Hydroxide" rather than N Sodium Hydroxide." USP 23 specifies that 0.30ml be used. The new method number is QS-236-02.

- QS test method QC-151-01 "Assay for Potassium Chloride Extended-release Tablets and Granules, Klor-Con® M20" was revised. To coincide with the assay specification which calls for a % KCl result, the mg KCl/g sample calculation was revised to % KCl. Also, in order to simplify the final calculations involved, the % labeled amount calculations were consolidated into one equation. A second revision was necessary to correct a typographical error. The new method number is QS-151-03.

- The raw material specification sheets for Croscarmellose Sodium, NF, Ethylcellulose, NF (Ethocel 20), Microcrystalline Cellulose, NF (Emocel 90M), and Sorbitan Monooleate, NF (Span 80) have all been updated per USP 23 Supplements 1-4. Updated specification sheets for these raw materials are provided.

This Amendment #007 is being submitted in duplicate for incorporation into our file.

As required per 21 CFR 314.50h(3), we hereby certify that a field copy of this Amendment #007 has been submitted to the Minneapolis District FDA for their review as well.

Should you have any questions regarding the information contained herein, please contact Dianne Gibbs, Regulatory Affairs Specialist at (612) 449-7261.

Sincerely,

UPSHER-SMITH LABORATORIES, INC.

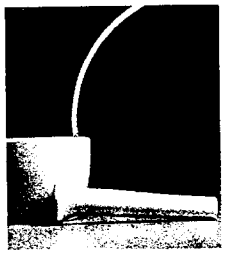
Mark S. Robbins

Mark S. Robbins, Ph.D.
Vice President, Scientific Affairs

MSR/DG/bac

enclosure

c: Mr. Paul Chapman
Project Officer
Center for Drug Evaluation and Research
Food and Drug Administration
HFD-53, Room 12A-43
5600 Fishers Lane
Rockville, MD 20857



Upsher-Smith Laboratories, Inc.
Innovative Pharmaceuticals Since 1919

June 26, 1996

FEDERAL EXPRESS

Dr. Keith Chan
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
HFD-650, Room E-130
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

Dear Dr. Chan:

RE: Amendment #006 to ANDA 74-726: Klor-Con® M20 (Potassium Chloride Extended-release Tablets, USP, 20 mEq) Additional In-Vitro Comparative Dissolution Data; Individual Tablet Data

Pursuant to our June 26, 1996, phone communication with Mr. Larry Galvin, Consumer Safety Officer, Division of Bioequivalence, submitted herewith are additional comparative dissolution data between Klor-Con® M20 and the reference product, K-DUR® 20. As requested, individual tablet data, along with standard deviations and ranges, are provided for the comparative dissolution studies conducted in water, submitted in the original ANDA.

This Amendment #006 is being submitted in duplicate for incorporation into our file.

Should you have any questions regarding these data or require additional information, please contact Dianne Gibbs, Regulatory Affairs Specialist at (612) 449-7261.

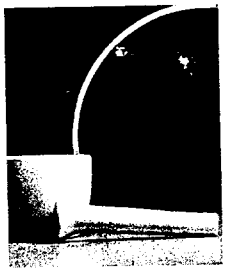
Sincerely,

UPSHER-SMITH LABORATORIES, INC.

Dianne Gibbs for

Mark S. Robbins, Ph.D.
Vice President, Scientific Affairs

MSR/bac



Upsher-Smith Laboratories, Inc.
Innovative Pharmaceuticals Since 1919

June 20, 1996

NEW CORRESP
NC
BIOAVAILABILITY

FEDERAL EXPRESS

Dr. Keith Chan
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
HFD-650, Room E-130
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

RECEIVED
JUN 21 1996
GENERIC DRUGS

Dear Dr. Chan:

RE: Amendment #005 to ANDA 74-726: Klor-Con® M20 (Potassium Chloride Extended-release Tablets, USP, 20 mEq) Additional In-Vitro Comparative Dissolution Data

Pursuant to recent phone communications with Mr. Larry Galvin, Consumer Safety Officer, Division of Bioequivalence, submitted herewith are additional comparative dissolution data between Klor-Con® M20 and the reference product, K-DUR® 20. As requested, these dissolutions were conducted using USP Apparatus II (Paddles) at 50 rpm, in simulated intestinal fluid without enzymes at 37°C.

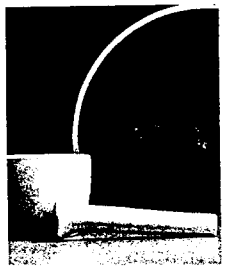
Should you have any questions regarding these data or require additional information, please contact Dianne Gibbs, Regulatory Affairs Specialist at (612) 449-7261.

Sincerely,

UPSHER-SMITH LABORATORIES, INC.

Mark S. Robbins, Ph.D.
Vice President, Scientific Affairs

MSR/bac



NO 7150
4/22/96

Upsher-Smith Laboratories, Inc.

Innovative Pharmaceuticals Since 1919

April 4, 1996

CERTIFIED MAIL/RETURN RECEIPT REQUESTED

RECEIVED

NEW CORRES
NC

APR 0 8 1996

GENERAL

Mr. Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, MD 20855

Dear Mr. Sporn:

RE: ANDA 74-726
Klor-Con® (Potassium Chloride Extended-release Tablet, USP, 20 mEq)
Intent to File Major Amendment

In regard to the letter written by Dr. Rashmikant Patel, Director, Division of Chemistry I, dated March 27, 1996, and received by Upsher-Smith Laboratories, Inc. , on April 2, 1996, we wish to avail ourselves of the opportunity per 21 CFR 314.120 (a) of filing a major amendment to the application addressing the items cited in the above-referenced letter.

This letter is being submitted in duplicate for incorporation into our file.

Sincerely,

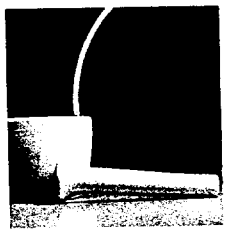
UPSHER-SMITH LABORATORIES, INC.

Mark S. Robbins

Mark S. Robbins, Ph.D.
Vice President, Scientific Affairs

MSR/bac

4-4-96



Upsher-Smith Laboratories, Inc.

Innovative Pharmaceuticals Since 1919

November 9, 1995

FEDERAL EXPRESS

NEW CORRESP
NC

Charles Ganley, M.D.
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II, HFD-600
7500 Standish Place
Rockville, MD 20855-2773

RECEIVED
NOV 13 1995
GENERIC DRUGS

Dear Dr. Ganley:

RE: Amendment #004 to ANDA 74-726: Klor-Con® M20 (Potassium Chloride Extended-release Tablets, USP, 20 mEq)
Documentation of Patent Certification Notice Receipt

Reference is made to the above referenced ANDA, dated August 8, 1995, file date October 13, 1995.

Reference is also made to Amendment #003 to ANDA 74-726 dated November 6, 1995. Amendment #003 provided certification that the owner of patent #4863743/holder of the approved listed drug, K-DUR® had been notified as of November 3, 1995 of patent non-infringement according to 21 CFR 314.95. A copy of the Patent Certification Notice, dated November 3, 1995 was provided as part of Amendment #003.

Per 21 CFR 314.95(e), submitted herewith is a copy of the certified mail return receipt documenting receipt of the Patent Certification Notice by Schering Plough Corporation. Although the date of delivery was not documented on the return receipt card, the signed return receipt card was received by Upsher-Smith on November 9, 1995.

This Amendment #004 is being submitted in duplicate for incorporation into our file.

Upsher-Smith certifies that a third (field) copy of this Amendment #004 to ANDA 74-726 has been sent to the Minneapolis District Office and that this third (field) copy is a "true" copy.

Should you have any questions or comments on the information provided herewith, please contact Dianne Gibbs, Regulatory Affairs Specialist at (612) 449-7261.

Sincerely,

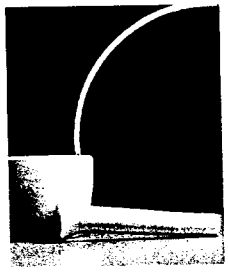
UPSHER-SMITH LABORATORIES, INC.

Mark S. Robbins

Mark S. Robbins, Ph.D.
Vice President, Scientific Affairs

MSR/bac

enclosure



Upsher-Smith Laboratories, Inc.
Innovative Pharmaceuticals Since 1919

noted NAP 8 Sheets 11/16/95

November 6, 1995

NEW CORRESP

NC

FEDERAL EXPRESS

Charles Ganley, M.D.
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II, HFD-600
7500 Standish Place
Rockville, MD 20855-2773

Dear Dr. Ganley:

RE: Amendment #003 to ANDA 74-726: Klor-Con® M20 (Potassium Chloride Extended-release Tablets, USP, 20 mEq)
Patent Certification Notice and Unit Dose Packaging Configuration

Reference is made to the above referenced ANDA, dated August 8, 1995, file date October 13, 1995.

Upsher-Smith Laboratories, Inc. hereby certifies that the owner of patent #4863743/holder of the approved listed drug, K-DUR® has been notified as of November 3, 1995 of patent non-infringement according to 21 CFR 314.95. Included herewith is a copy of the Patent Certification Notice, dated November 3, 1995.

Also submitted herewith are the unit dose packaging configuration diagrams for the Klor-Con® M20 unit dose package.

This Amendment #003 is being submitted in duplicate for incorporation into our file.

RECEIVED

NOV 0 8 1995

GENERIC DRUGS

6 Nov 95

UPSHER-SMITH

14905 23rd Avenue North Minneapolis, MN USA 55447-4709
Corporate Headquarters 612-473-4412 FAX# 612-476-4026 Sales & Distribution 1-800-654-2299

Upsher-Smith certifies that a third (field) copy of this Amendment #003 to ANDA 74-726 has been sent to the Minneapolis District Office and that this third (field) copy is a "true" copy.

Should you have any questions or comments on the information provided herewith, please contact Dianne Gibbs, Regulatory Affairs Specialist at (612) 449-7261.

Sincerely,

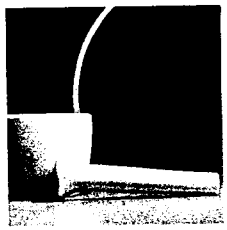
UPSHER-SMITH LABORATORIES, INC.

Dianne Gibbs for

Mark S. Robbins, Ph.D.
Vice President, Scientific Affairs

MSR/bac

enclosure



Upsher-Smith Laboratories, Inc.

Innovative Pharmaceuticals Since 1919

October 12, 1995

FEDERAL EXPRESS

NDA ORIG AMENDMENT

Charles Ganley, M.D.
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II, HFD-600
7500 Standish Place
Rockville, MD 20855-2773

Dear Dr. Ganley:

RE: Amendment 002 to ANDA 74-726: Klor-Con® M20 (Potassium Chloride Extended-release Tablets, USP, 20 mEq)
Response to Agency's October 3, 1995 Refuse to File Notice

Reference is made to the above referenced ANDA, dated August 8, 1995.

Reference is also made to the Agency's second Refusal to File notice dated October 3, 1995.

Pursuant to the Agency's comment in the above referenced Refusal to File notice, Upsher-Smith Laboratories, Inc. hereby withdraws the Klor-Con® M10 tablet formulation from ANDA 74-726. All references to the Klor-Con® M10 tablet formulation should be disregarded. All labeling comparisons and draft labeling for the Klor-Con® M10 tablet should be disregarded as well.

Submitted herewith in support of full review of the Klor-Con® M20 tablet formulation, is a revised package insert labeling comparison, comparing the latest approved package insert for the reference drug, K-DUR® to the proposed generic drug, Klor-Con® M20 tablets. This labeling comparison has been annotated to show differences between K-DUR®'s package insert and the Klor-Con® M20 package insert, as well as those changes made to the Klor-Con® M20 package insert to delete all references to the Klor-Con® M10 tablet formulation. A revised draft package insert for the proposed generic drug, Klor-Con® M20 tablet has been included as well.

RECEIVED

OCT 13 1995

GENERIC DRUGS

3

UPSHER-SMITH

14905 23rd Avenue North Minneapolis, MN USA 55447-4709
Corporate Headquarters 612-473-4412 FAX# 612-476-4026 Sales & Distribution 1-800-654-2299

Upsher-Smith believes that based on the deletion of the Klor-Con® M10 formulation from the ANDA and submission of the revised package insert, ANDA 74-726 for Klor-Con® M20 (Potassium Chloride Extended-release Tablets, USP, 20 mEq) is sufficiently complete to merit critical technical review.

This response is being submitted in duplicate for incorporation into our file. Four additional copies of the revised draft package insert are included as well.

As required per 21 CFR 314.50h(3), we hereby certify that a third (field) copy of this Amendment 002 to ANDA 74-726 has been sent to the Minneapolis District office and that this third (field) copy is a "true" copy.

Should you have any questions or comments on the information provided herewith, please contact Dianne Gibbs, Regulatory Affairs Specialist, at (612) 449-7261.

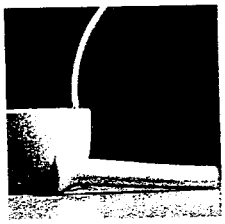
Sincerely,

UPSHER-SMITH LABORATORIES, INC.

Mark S. Robbins, Ph.D.
Vice President, Scientific Affairs

MSR/bac

enclosures



Refuse to file
9/18/95

Upsher-Smith Laboratories, Inc.

Innovative Pharmaceuticals Since 1919

September 11, 1995

FEDERAL EXPRESS

NDA ORIG AMENDMENT
AC

RECEIVED
SEP 12 1995
GENERIC DRUGS

Roger Williams, M.D.
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II, HFD-600
7500 Standish Place
Rockville, MD 20855-2773

Dear Dr. Williams:

RE: Amendment 001 to ANDA 74-726: Klor-Con® M10 and Klor-Con® M20 (Potassium Chloride Extended-release Tablets, USP, 20 mEq)
Response to Agency's August 28, 1995 Refuse to File Notice

Reference is made to the above referenced ANDA, dated August 8, 1995.

Reference is also made to the Agency's Refusal to File notice dated August 28, 1995.

Pursuant to the Agency's comments in the above referenced Refusal to File notice, the following information is submitted:

- A revised Paragraph IV Patent Certification certifying that the manufacture, use, or sale of Klor-Con® M Tablets will not infringe on Key Pharmaceutical's method of use patent, U-99 (method of providing potassium to a subject in need of potassium), #4863743, expiring September 5, 2006, for the reference listed drug.

  Per 21 CFR 314.95(a) and (b), Upsher-Smith Laboratories, Inc. certifies that the owner of patent #4863743, as well as Key Pharmaceuticals, holder of the approved listed drug, K-DUR®, will be notified of patent non-infringement according to the requirements under 21 CFR 314.95(c) upon Upsher-Smith receiving notification that the FDA has found the application acceptable for filing.

- A revised certification statement with an original signature certifying that a third (field) copy of the technical sections of the ANDA **has been** sent to the Minneapolis District Office and that this field copy is a "true" copy.

Upsher-Smith acknowledges the Agency's comment regarding the unacceptability of the *in-vivo* bioequivalence waiver for the mEq strength of Klor-Con® M tablets under 21 CFR 320.22(d)(2)(iv), which excludes controlled release dosage forms from the *in-vivo* waiver request provision. In response, we would like to point out that the listed drug, K-DUR® mEq Tablets were granted approval based on dosage proportionality alone. No clinical studies or bioavailability studies were conducted by the innovator on K-DUR® mEq tablets. Furthermore, we feel that information included in our request for waiver of *in-vivo* bioequivalence submitted as Section VI.B. of the ANDA supports granting the waiver. We, therefore, request full review of the request for waiver by the Division of Bioequivalence.

This response is being submitted in duplicate for incorporation into our file.

Upsher-Smith certifies that a third (field) copy of this amendment 001 to ANDA 74-726 has been sent to the Minneapolis District Office and that this third (field) copy is a "true" copy.

Should you have any questions or comments on the information provided herewith, please contact Dianne Gibbs, Regulatory Affairs Specialist, at (612) 449-7261.

Sincerely,

UPSHER-SMITH LABORATORIES, INC.

Mark S. Robbins

Mark S. Robbins, Ph.D.
Vice President, Scientific Affairs

MSR/bac

enclosures

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

APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314)

Form Approved: OMB No. 0910-0001
Expiration Date; August 31,1989.

FOR FDA USE ONLY

DATE RECEIVED	DATE FILED
DIVISION ASSIGNED	**NDA/ANDA NO. ASS.**

NOTE: No application may be filed unless a completed application form has been received *(21 C.F.R. Part 314).*

NAME OF APPLICANT
Upsher-Smith Laboratories, Inc.

DATE OF SUBMISSION
September 11, 1995

TELEPHONE NO. *(Include Area Code)*
(612) 473-4412

ADDRESS *(Number, Street, City, State and Zip Code)*
14905 23rd Avenue North
Minneapolis, Minnesota 55447

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER (If previously issued)
74-726

DRUG PRODUCT

ESTABLISHED NAME *(e.g., USP/USAN)*
Potassium Chloride Extended-release Tablets, USP

PROPRIETARY NAME *(If any)*
Klor-Con^{R} M20

CODE NAME *(If any)*
N/A

CHEMICAL NAME
Potassium Chloride

DOSAGE FORM	ROUTE OF ADMINISTRATION	STRENGTH(S)
Tablet	Oral	20 mEq

PROPOSED INDICATIONS FOR USE
Potassium Supplementation

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, AND DRUG MASTER FILES *(21CFR 314.420)* REFERRED TO IN THIS APPLICATION:
N/A

INFORMATION ON APPLICATION

TYPE OF APPLICATION *(Check one)*

☐ THIS SUBMISSION IS A FULL APPLICATION *(21 CFR 314.50)* ☒ THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) (21 CFR 314.55)

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG	HOLDER OF APPROVED APPLICATION
20 mEq Tablets	Schering

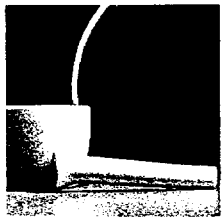
STATUS OF APPLICATION *(Check one)*

☐ PRESUBMISSION
☐ ORIGINAL APPLICATION
☒ AN AMENDMENT TO A PENDING APPLICATION
☐ RESUBMISSION
☐ SUPPLEMENTAL APPLICATION

PROPOSED MARKETING STATUS *(Check one)*

☒ APPLICATION FOR A PRESCRIPTION DRUG PRODUCT *(Rx)*
☐ APPLICATION FOR AN OVER - THE - COUNTER PRODUCT *(OTC)*

FORM FDA 356h (3/87)



Upsher-Smith Laboratories, Inc.

Innovative Pharmaceuticals Since 1919

Paragraph IV Patent Certification

September 11, 1995

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Room 150
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

To Whom It May Concern:

RE: Listed Drug Product: Key Pharmaceutical's K-DUR®, Potassium Chloride Extended-release Tablets, USP, 20mEq

Pursuant to Section 505(j)(2)(A)(vii) of the Federal Food, Drug and Cosmetic Act, Upsher-Smith Laboratories, Inc., hereby certifies that the method of use patent, U-99 (method of providing potassium to a subject in need of potassium), #4863743, expiring September 5, 2206 for the reference listed drug will not be infringed by the manufacture, use, or sale of the new drug, Klor-Con® M Tablets for which the application is submitted.

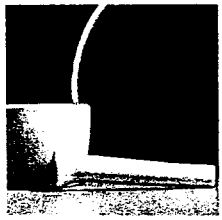
Pursuant to 21 CFR 314.95(a) and (b), Upsher-Smith hereby certifies that the owner of patent #4863743, as well as Key Pharmaceuticals, holder of the approved listed drug, K-DUR®, will be notified of non-infringement of the above referenced patent according to the requirement under 21 CFR 314.95(c) upon Upsher-Smith receiving notification that FDA has found the application acceptable for filing.

Sincerely,

UPSHER-SMITH LABORATORIES, INC.

Mark S. Robbins, Ph.D.
Vice President, Scientific Affairs

MSR/bac



Upsher-Smith Laboratories, Inc.

Innovative Pharmaceuticals Since 1919

September 11, 1995

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Room 150
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

To Whom It May Concern:

RE: ANDA 74-726 - Klor-Con® M10 and Klor-Con® M20 (Potassium Chloride Extended-release Tablets, USP, 20 mEq)

As required per 21 CFR 314.50(h)(3), we hereby certify that a field copy of the Chemistry, Manufacturing and Controls sections of the above referenced ANDA has been sent to the Minneapolis District Office for their review. This third (field) copy is a "true" copy of the technical sections of the application.

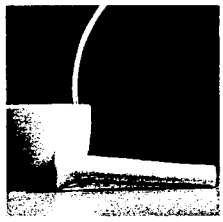
Sincerely,

UPSHER-SMITH LABORATORIES, INC.

Mark S. Robbins

Mark S. Robbins, Ph.D.
Vice President, Scientific Affairs

MSR/bac



Upsher-Smith Laboratories, Inc.
Innovative Pharmaceuticals Since 1919

8/17/95

8/21/95

August 8, 1995

CERTIFIED MAIL/RETURN RECEIPT REQUESTED

Roger Williams, M.D.
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II, HFD-600
7500 Standish Place
Rockville, MD 20855-2773

Dear Dr. Williams:

RE: Original Abbreviated New Drug Application (ANDA) for Klor-Con® M20 (Potassium Chloride Extended-release Tablets, USP, 20 mEq)

Submitted herewith, please find an original ANDA for Klor-Con® M20 Tablets (Potassium Chloride Extended-release Tablets, USP). This drug is the same as the reference drug, K-DUR® (Potassium Chloride Extended-release Tablets, USP), Schering NDA 19-439.

Upsher-Smith Laboratories, Inc. (the ANDA applicant) is located at:

14905 23rd Avenue North
Minneapolis, MN 55447
Phone: (612) 473-4412
FAX: (612) 476-4026

This original ANDA is being submitted, in duplicate, as an archival and review copy. The archival copy (blue jackets) consists of 14 volumes. The review copy contains two parts; the chemistry, manufacturing and controls data consisting of 3 volumes (red jackets), and the bioavailability/bioequivalence data consisting of 11 volumes (orange jackets).

The bioequivalence study report is provided on disk in WordPerfect format. Clinical data tables D1-D46 are also provided on disk in ASCII format. This disk is submitted in the front of Section VI (Volume 2) of this application.

As required per 21 CFR 314.50h(3), we hereby certify that a field copy is being submitted to the Minneapolis District Office for their review as well.

Should you have any questions or comments regarding this supplement, please call Dianne Gibbs, Regulatory Affairs Specialist at (612) 449-7261.

Sincerely,

UPSHER-SMITH LABORATORIES, INC.

Mark S. Robbins

Mark S. Robbins, Ph.D.
Vice President, Scientific Affairs

MSR/DG/bac

c: Food and Drug Administration
Minneapolis District Office
240 Hennepin Avenue
Minneapolis, MN 55401

enclosure