CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-092

CORRESPONDENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Office of the Chief Mediator and Ombudsman
Food and Drug Administration
5600 Fishers Lane
Room 14-105, HF-7
Rockville, MD 20857

October 19, 1998

Mr. Martin A. Baker
Vice President
Metabolic Solutions, Inc.
7 Henry Clay Drive
Merrimack, NH 03054

Re: Prescription Drug User Fee Act
Small Business Waiver Request
Our file number: 99.004 (formerly 98.068)

Dear Mr. Baker:

This letter responds to your August 13, 1998 letter on behalf of Metabolic Solutions, Inc. (Metabolic Solutions), requesting a waiver of the fiscal year (FY) 1999 application fee assessable upon submission of the new drug application for ^{13}C-Urea Blood Test (Ez-HBT™), as prescribed by the small business waiver provision of the Prescription Drug User Fee Act as amended by the Food and Drug Administration Modernization Act of 1997 (User Fee Act), 21 U.S.C. § 379h(d)(1)(E). For reasons stated below, the Food and Drug Administration (FDA) grants Metabolic Solutions' request for a waiver of the application fee.

The small business waiver provision entitles a qualified small business to a waiver of the application fee when the business meets two criteria: first, a business must employ fewer than 500 persons, including employees of affiliates; and second, the marketing application must be the first human drug application that a company or its affiliate submits to FDA for review, 21 U.S.C. § 379h(d)(3).

FDA's decision to grant a small business waiver to Metabolic Solutions is based on two findings. First, by letter dated September 30, 1998, the Small Business Administration (SBA) determined that, as of September 2, 1998, Metabolic Solutions employed fewer than 500 persons and had no

affiliates. Second, according to FDA records, the marketing application for Ez-HBT™ is the first human drug application, within the meaning of the User Fee Act, to be submitted to FDA by Metabolic Solutions.

Therefore, FDA grants Metabolic Solutions a waiver of the application fee covering Ez-HBT™, provided that FDA receives the marketing application not later than March 2, 1999, six months after the effective date of the size determination made by SBA. If Metabolic Solutions is unable to meet this time limit, it should contact this office for information about the process for extending the period during which a marketing application may be submitted without the need to submit a new waiver request. In addition, once the marketing application has been received by FDA, if FDA refuses to file the marketing application, or if Metabolic Solutions withdraws the marketing application before it is filed by FDA, Metabolic Solutions should contact this office, approximately 90 days before it expects to resubmit the marketing application covering Ez-HBT™, for information about the process for determining whether Metabolic Solutions continues to qualify for a small business waiver.

FDA's Office of Financial Management and the Center for Drug Evaluation and Research (CDER) which are responsible for the collection and assessment of fees, respectively, have been notified of this waiver. Billing questions should be directed to Mr. Michael Jones, CDER, at 301-594-2041.

Please note that FDA plans to disclose information about its actions granting or denying waivers, consistent with the laws and regulations governing the disclosure of confidential commercial or financial information.

Please include a copy of this letter in the marketing application for Ez-HBT™. If you have any questions about this small business waiver, please contact Ms. Kathleen Locke, of this office, at 301-827-3390.

Sincerely yours,

/S/

Suzanne M. O'Shea
Office of the Chief Mediator and Ombudsman
Deputy User Fee Waiver Officer

Boston University

Community Technology Fund
108 Bay State Road
Boston, Massachusetts 02215

617/353-4550
Fax: 617/353-6141

Ashley J. Stevens, D.Phil (Oxon)
Director, Office of Technology Transfer
Direct line: (617) 353-6303
Email: astevens@bu.edu

January 8, 1999

By Facsimile: (603) 598-6973

Martin A. Baker
Vice President
Metabolic Solutions, Inc.
460 Amherst Street
Nashua, NH 03063

Dear Martin:

RE: License Agreement dated January 21, 1997 with Trustees of Boston University, also acting as agent for Regents of University of California

This it to confirm that US Patent 5,542,419, "Noninvasive Method to Detect Gastric *Helicobacter Pylori*" is co-owned by Boston University, by assignment from Robert Michener, and the University of California, by assignment from Rex Moulton-Barrett. Pursuant to an inter-institutional agreement between Boston University and the University of California dated March 24, 1994, which appointed Boston University the agent of the University of California, Boston University granted Metabolic Solutions an exclusive license to this patent for all uses, effective January 21, 1997.

As of the date above, the license is in good standing, with all the licensee's obligations current and having been met in full.

Any questions concerning this license should be addressed to the undersigned at the number above.

Yours sincerely,

cc Matt Burns
Ed Lusardi/Company File

VOLUME 1

APPENDIX E-1 1=

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Office of the Chief Mediator and Ombudsman
5600 Fishers Lane (HF-7)
Room 14-105
Rockville, MD 20857

Food and Drug Administration
Rockville MD 20857

March 2, 1999

Martin A. Baker
Vice President
Metabolic Solutions, Inc.
460 Amherst Street
Nashua, NH 03063

Re: Prescription Drug User Fee Act
Small Business Waiver Extension
Our File: 99.004

Dear Mr. Baker:

This letter responds to your letter, dated February 22, 1999, on behalf of Metabolic Solutions, Inc. (Metabolic Solutions) requesting an extension of the small business waiver granted to Metabolic Solutions by the Food and Drug Administration (FDA) on October 19, 1998. For reasons stated below, FDA grants Metabolic Solutions an extension of its small business waiver.

The small business waiver provision of the Prescription Drug User Fee Act[1] (User Fee Act) entitles a qualified small business to a waiver of the application fee when the business meets two criteria: first, a business must have fewer than 500 employees, including employees of affiliates; and second, the marketing application must be the first human drug application that a company or its affiliate submits to FDA for review.[2]

FDA's decision to grant Metabolic Solutions a small business waiver was based on two findings: First, by letter dated September 30, 1998, the Small Business Administration (SBA) determined that, as of September 2, 1998, Metabolic Solutions employed fewer than 500 persons and had no affiliates. Second, according to FDA records, the marketing application for Ez-HBT is the first human drug application, within the meaning of the User Fee Act, to be submitted to FDA by Metabolic Solutions.

On October 19, 1998 FDA granted Metabolic Solutions a waiver of the application fee covering ^{13}C-Urea Blood Test (Ez-HBT), provided that FDA received the marketing application not later than March 2, 1999, six months after the effective date of the size determination. Metabolic Solutions does not expect to be able to meet this time limit and

[1] 21 U.S.C. § 379g et seq.
[2] 21 U.S.C. § 379h(d)(3)

now requests an extension of its small business waiver for Ez-HBT (NDA 21-092). In support of its request for an extension, Metabolic Solutions certifies that since September 2, 1998 (effective date of the size determination) there have been "no material changes" to the company (economic or employment) that would effect its status as a small business. The company states that it has nine employees, continues to have no affiliates, and that NDA 21-092 will still be its first application.

Based on the facts as certified by Metabolic Solutions, FDA agrees to extend the small business waiver for an additional six months. Therefore, FDA grants Metabolic Solutions a waiver of the application fee covering Ez-HBT, provided that FDA receives the marketing application not later than September 2, 1999, one year from the effective date of the size determination.

If Metabolic Solutions is unable to meet this extended time limit, it should consult this office regarding the process for determining whether Metabolic Solutions continues to qualify for a small business waiver. In addition, once the marketing application has been received by FDA, if FDA refuses to file the marketing application, or if Metabolic Solutions withdraws the marketing application before it is filed by FDA, Metabolic Solutions should contact this office, approximately 90 days before it expects to resubmit the marketing application for Ez-HBT, for information about the process for determining whether Metabolic Solutions continues to qualify for a small business waiver.

FDA's Office of Financial Management and the Center for Drug Evaluation and Research (CDER) which are responsible for the collection and assessment of fees, respectively, have been notified of this waiver. Billing questions should be directed to Mr. Michael Jones, CDER, at 301-594-2041.

Please note that FDA plans to disclose information about its actions granting or denying waivers, consistent with the laws and regulations governing the disclosure of confidential commercial or financial information.

Please include a copy of this letter in the marketing application covering Ez-HBT. If you have any questions about this matter, please contact Ms. Kathleen Locke, of this office, at 301-827-3390.

Sincerely yours,

/S/

Suzanne M. O'Shea
Deputy User Fee Waiver Officer
Office of the Chief Mediator and Ombudsman

Metabolic Solutions Inc.

460 Amherst Street
Nashua, NH 03063
(603) 598-6960 Phone
(603) 598-6973 Fax

Internet: http://www.metsol.com
E-mail: metsol@earthlink.net

March 17, 1999

Center for Drug Evaluation and Research
Food and Drug Administration
Document and Records Section
12229 Wilkins Avenue
Rockville, MD 20852

Good Morning,

Enclosed is an original application (NDA #21-092) for our drug product Helicosol/device Ez-HBT Helicobacter Blood Test. We have enclosed an archival copy, technical copies (chemistry, pharmacology, pharmacokinetics, clinical studies, and statistics) and a field copy of the chemistry section. Also enclosed are 3 desk copies for Robin Anderson (our liaison with CDER). In addition, several CDER reviewers in a conference call, asked for electronic copies of certain sections. The disks are labeled, chemistry section, clinical studies (text), clinical studies tabular data (spreadsheet) and labeling.

Under separate cover, we have sent the 510K application for our device (Ez-HBT Helicobacter Blood Test) to the Center for Devices and Radiological Health.

Included in the archival copy is the user fee cover sheet and waiver, disclosure of financial interests, debarment certification, patent certification and field copy certification. All clinical studies were conducted under good clinical practices and following the Agency's informed consent regulations (21 CFR part 50).

Thank you for consideration of this application.

Sincerely,

David A. Wagner, Ph.D.
President

HFI 590 1444

APR 5 1999

Metabolic Solutions, Inc.
Attention: David A. Wagner, Ph.D.
460 Amherst Street
Nashua, NH 03063

Dear Dr. Wagner:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Helicosol (C^{13}-urea) lyophilized powder

Therapeutic Classification: Standard (S)

Date of Application: March 17, 1999

Date of Receipt: March 19, 1999

Our Reference Number: 21-092

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on May 18, 1999 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be January 19, 2000 and the secondary user fee goal date will be March 19, 2000.

As of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within 120 days of receipt of your pediatric drug development plan, we will notify you of the pediatric studies that are required under section 21 CFR 314.55.

If you believe that this drug qualifies for a waiver of the study of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 10 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov.cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" in addition to your plans for pediatric drug development described above. If you do not submit a Proposed Pediatric Study Request within 120 days from the date of this letter, we will presume that you are not interested in obtaining pediatric exclusivity and will notify you of the pediatric studies that are required under section 21 CFR 314.55. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Special Pathogen and
Immunologic Drug Products, HFD-590
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Special Pathogen and
Immunologic Drug Products, HFD-590
Attention: Division Document Room
9201 Corporate Blvd.
Rockville, Maryland 20850-3202

If you have any questions, contact Robin Anderson, Project Manager, at (301) 827-2127.

Sincerely,

/S/

Ellen C. Frank, R.Ph.
Chief, Project Management Staff
Division of Special Pathogen and Immonulogic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

ORIGINAL
BM

460 Amherst Street
Nashua, NH 03063
(603) 598-6960 Phone
(603) 598-6973 Fax

Internet: http://www.metsol.com
E-mail: metsol@earthlink.net

May 4, 1999

Mark J. Goldberger, M.D.
Director, Division of Special Pathogens and
Immunologic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-590
Rockville, MD 20850

ORIG AMENDMENT

Re: NDA 21-092 (Helicosol)

Dear Dr. Goldberger,

Please include this supplemental information in our NDA Application 21-092 that was requested by telephone conversation with Robin Anderson on 5/3/99 as well as fax dated 5/4/99 from her.

1. The completion date for our clinical studies of efficacy and safety of Helicosol and the Ez-HBT medical device was November 17, 1998. No further clinical studies were conducted beyond this date.

2. There were no non-clinical studies conducted in support of NDA Application 21-092 as described in the definitions of 21 CFR Part 58, "Good Laboratory Practice for Nonclinical Laboratory Studies". The non-clinical studies required for a New Drug Application (i.e. toxicology, pharmacology and pharmacokinetics) were described in the application from previous scientific literature references. Thus, for this application, 21 CFR Part 58, does not apply.

3. We would like to confirm that all clinical studies in support of NDA Application 21-092 were conducted using the ethical principles governing research involving human subjects outlined by the World Medical Association Declaration of Helsinki, adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964 and amended in 1975, 1983 and 1989.

4. We are including a re-format of the clinical data for Protocols HBT-03 and Protocol HBT-03-Cutoff as suggested by FDA Clinical reviewers.

5. We are submitting copies of scientific literature requested by FDA Biopharmacology reviewers, references 59, 61, 62, 63, 65, 66, 67, 68, and 69.

460 Amherst Street
Nashua, NH 03063
(603) 598-6960 Phone
(603) 598-6973 Fax

Internet: http://www.metsol.com
E-mail: metsol@earthlink.net

6. In Volume 2, page 2-103 we have discussed the Environmental Impact of Helicosol. Our original application claimed a categorical exclusion from the environmental impact assessment under 21 CFR 25.31(c). As was correctly pointed out by Chemistry Review, ^{13}C-urea drug substance is synthesized thus 21 CFR 25.31 (c) exclusion does not apply. We now wish to revise our claim for a categorical exclusion from the environmental assessment under 21 CFR 25.31 (b). Based on the projected marketing expectations for the product, this action will increase the use of the active moiety (^{13}C-urea) but the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 parts per billion.

This completes the supplemental information requested by Robin Anderson. If there is addition information needed or questions about the supplemental information, please don't hesitate to call me at 603-598-6960.

Sincerely,

David A. Wagner, Ph.D.
President

ORIGINAL

BM

etabolic
olutions
Inc.

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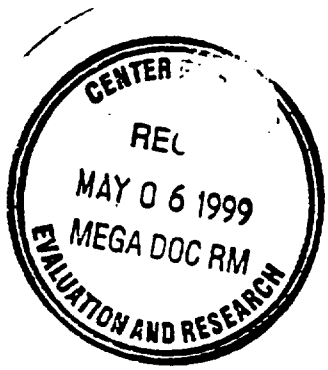
May 5, 1999

Document Control Room
Division of Special Pathogens and
Immunologic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-590
Rockville, MD 20850



Re: NDA 21-092 (Helicosol)

Good Morning,

Please include this supplemental information in our NDA Application 21-092 that was requested by Robin Anderson of your division. There are 3 copies of this supplemental information in the package.

Sincerely,

David A. Wagner, Ph.D.
President

ORIGINAL

BC

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utions
Inc.

460 Amherst Street
Nashua, NH 03063
(603) 598-6960 Phone
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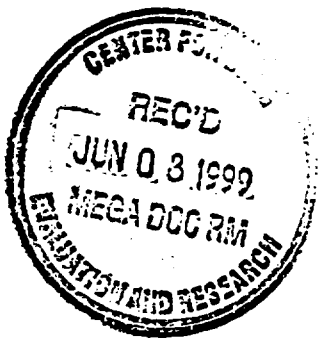
June 7, 1999

ORIG AMENDMENT



Mark J. Goldberger, M.D.
Director, Division of Special Pathogens and
Immunologic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-590
Rockville, MD 20850

Re: NDA 21-092 (Helicosol)

Dear Dr. Goldberger,

Please include this supplemental information in our NDA Application 21-092. This supplement contains 9 month real time stability data for our product Helicosol that was not included in our original application.

If there is addition information needed or questions about the supplemental information, please don't hesitate to call me at 603-598-6960.

Sincerely,

David A. Wagner, Ph.D.
President

MJ

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

SEP 24 1999

David A. Wagner, Ph.D.
President
Metabolic Solutions, Inc.
460 Amherst Street
Nashua, New Hampshire 03063

Re: K990931
Trade Name: Ez-HBT Helicobacter Blood Test
Regulatory Class: I
Product Code: MSQ
Dated: July 12, 1999
Received: July 13, 1999

Dear Dr. Wagner:

We have reviewed your Section 510(k) notification of intent to market the device referenced above and we have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (the Act). You may, therefore, market the device, subject to the general controls provisions of Act. However, you are responsible to determine that the medical devices you use as components in the kit have either been determined as substantially equivalent under the premarket notification process (Section 510(k) of the act), or were on the market prior to May 28, 1976, the enactment date of the Medical Device Amendments. Please note: If you purchase your device components in bulk (i.e., unfinished) and further process (e.g., sterilize) you must submit a new 510(k) before including these components in your kit. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into either class II (Special Controls) or class III (Premarket Approval) it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 895. A substantially equivalent determination assumes compliance with the Current Good Manufacturing Practice requirements, as set forth in the Quality System Regulation (QS) for Medical Devices: General regulation (21 CFR Part 820) and that, through periodic QS inspections, FDA will verify such assumptions. Failure to comply with the GMP regulation may result in regulatory action. In addition, the Food and Drug Administration (FDA) may publish further announcements concerning your device in the Federal Register. Please note: this response to your premarket notification submission does not affect any obligation you might have under sections 531 through 542 of the Act for devices under the Electronic Product Radiation Control provisions, or other Federal laws or regulations.

In addition, we have determined that your device kit contains Helicosol™ (125mg ^{13}C-urea lyophilized powder) which are subject to regulation as a drug.

Our substantially equivalent determination does not apply to the drug component of your device. We recommend you first contact the Center for Drug Evaluation and Research before marketing your device with the drug component (NDA 21-092). For information on applicable Agency requirements for marketing this drug, we suggest you contact:

Mark Goldberger, M.D., M.P.H.
Director, Division of Drug Labeling Compliance (HFD-310)
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857
(301) 827-2366

This letter will allow you to begin marketing your device as described in your 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801 and additionally 809 for in vitro diagnostic devices), please contact the Office of Compliance at (301) 594-4588. Additionally, for questions on the promotion and advertising of your device, please contact the Office of Compliance at (301) 594-4639. Also, please note the regulation entitled, "Misbranding by reference to premarket notification"(21 CFR 807.97). Other general information on your responsibilities under the Act, may be obtained from the Division of Small Manufacturers Assistance at its toll free number (800) 638-2041 or (301) 443-6597, or at its internet address "http://www.fda.gov/cdrh/dsma/dsmamain.html".

Sincerely yours,

/S/

Steven I. Gutman, M.D. M.B.A.
Director
Division of Clinical Laboratory Devices
Office of Device Evaluation
Center for Devices and Radiological Health

Enclosure

510(k) Number: K990931

Device Name: Ez-HBT Helicobacter Blood Test

Indications for Use:

The Ez-HBT™ Helicobacter Blood Test is intended for use in the qualitative detection of $^{13}CO_2$ in whole blood specimens, collected after the ingestion of ^{13}C-urea. Helicobacter pylori (*H. pylori*) organisms colonizing the lining of the human stomach, produce urease which converts ^{13}C-urea into $^{13}CO_2$ and ammonia (NH_4^+). The device is indicated as an aid in the diagnosis of *H. pylori* infection in symptomatic adult subjects, 18 years or older. For use by health care professionals. Administer test under a physician's supervision. Metabolic Solutions, Inc. or a qualified laboratory using Gas Isotope Ratio Mass Spectrometry or equivalent instrumentation must analyze the test samples.

(PLEASE DO NOT WRITE BELOW THIS LINE - CONTINUE ON ANOTHER PAGE IF NECESSARY)

Concurrence of CDRH, Office of Device Evaluation (ODE)

/S/

(Division Sign-Off)
Division of Clinical Laboratory Devices
510(k) Number K990931

Prescription Use X OR Over-The-Counter Use _____
(Per 21 CFR 801.109)

Metabolic Solutions Inc.

460 Amherst Street
Nashua, NH 03063
(603) 598-6960 Phone
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E-mail: metsol@earthlink.net

December 15, 1999

Jeff Fritsch
Division of Special Pathogens and
Immunologic Drug Products
Food and Drug Administration
9201 Corporate Boulevard, HFD-590, Rm. S-416
Rockville, MD 20850

Re: NDA 21-092 (Helicosol)

Dear Jeff,

I am sending 3 copies of the text of the final labeling for NDA # 21-092. There are 3 different labels which are named (1) the package insert, (2) unit dose label and (3) diagnostic kit label. This information has also been sent to the document room (i.e. Dr. Goldberger).

If there is addition information needed or questions about the supplemental information, please don't hesitate to call me at 603-598-6960.

Sincerely,

David A. Wagner, Ph.D.
President