

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-092

ADMINISTRATIVE DOCUMENTS



**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

New Drug Application (NDA # 21-092)
Carbon-13 (^{13}C) Urea Component

Patent Certification

Metabolic Solutions, Inc. has secured the exclusive rights to the following patent:

United States Patent Number: 5,542,419 Noninvasive Method to
Detect Gastric Helicobacter pylori, issued to Rex Moulton-Barrett and
Robert Michener, August 6, 1996 expiring August 15, 2013.

The undersigned declares that United States Patent Number 5,542,419 covers the formulation, composition and method of use of Carbon-13 or ^{13}C Urea in conjunction with a blood test. This product is a component of the subject of this application for which approval is being sought.



David A. Wagner

President

Metabolic Solutions, Inc.

Exclusivity Checklist

NDA:	21-092		
Trade Name:	Helicosal		
Generic Name:	C-13 Urea, lyophilized		
Applicant Name:	Metabolic Solutions, Inc		
Division:	HFD-590		
Project Manager:	JEFF FRITSCH		
Approval Date:			
PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?			
1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.			
a. Is it an original NDA?	Yes	<input checked="" type="checkbox"/>	No
b. Is it an effectiveness supplement?	Yes	<input type="checkbox"/>	No <input checked="" type="checkbox"/>
c. If yes, what type? (SE1, SE2, etc.)			
Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")			
	Yes	<input checked="" type="checkbox"/>	No
If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.			
Explanation:			
If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:			
Explanation:			
d. Did the applicant request exclusivity?	Yes	<input checked="" type="checkbox"/>	No
If the answer to (d) is "yes," how many years of exclusivity did the applicant request?			3 years
IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS.			
2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?			
	Yes	<input type="checkbox"/>	No <input checked="" type="checkbox"/>
If yes, NDA #			
Drug Name:			
IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE			

BLOCKS.			
3. Is this drug product or indication a DESI upgrade?	Yes	No	<input checked="" type="checkbox"/>
IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS (even if a study was required for the upgrade).			
PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES			
(Answer either #1 or #2, as appropriate)			
1. Single active ingredient product.	Yes	<input checked="" type="checkbox"/>	No
Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.	Yes	<input checked="" type="checkbox"/>	No
If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).			
Drug Product	Meretek UBT Kit " Urea C-13		
NDA #	20-586		
Drug Product	Pylori-Chek Breath Test " Urea C-13		
NDA #	20-900		
Drug Product			
NDA #			
2. Combination product.	Yes	No	<input checked="" type="checkbox"/>
If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing <u>any one</u> of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)	Yes	No	
If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).			
Drug Product			
NDA #			
Drug Product			
NDA #			
Drug Product			
NDA #			
IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY			

TO THE SIGNATURE BLOCKS. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.	Yes	<input checked="" type="checkbox"/>	No
--	-----	-------------------------------------	----

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application. For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?	Yes	<input checked="" type="checkbox"/>	No
--	-----	-------------------------------------	----

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCKS.**

Basis for conclusion:

b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?	Yes	<input checked="" type="checkbox"/>	No
---	-----	-------------------------------------	----

1) If the answer to 2 b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.	Yes	No	<input checked="" type="checkbox"/>
--	-----	----	-------------------------------------

If yes, explain:

2) If the answer to 2 b) is "no," are you aware of published

studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?	Yes	No	<input checked="" type="checkbox"/>
If yes, explain:			
c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:			
Investigation #1, Study #:	HBT-03-CUTOFF		
Investigation #2, Study #:	HBT-03		
Investigation #3, Study #:			
3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.			
a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")			
Investigation #1	Yes	No	<input checked="" type="checkbox"/>
Investigation #2	Yes	No	<input checked="" type="checkbox"/>
Investigation #3	Yes	No	<input type="checkbox"/>
If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:			
Investigation #1 -- NDA Number			
Investigation #2 -- NDA Number			
Investigation #3 -- NDA Number			
b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?			
Investigation #1	Yes	No	<input checked="" type="checkbox"/>
Investigation #2	Yes	No	<input checked="" type="checkbox"/>
Investigation #3	Yes	No	<input type="checkbox"/>
If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:			
Investigation #1 -- NDA Number			
Investigation #2 -- NDA Number			
Investigation #3 -- NDA Number			
If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):			
Investigation #1	HBT-03-CUTOFF		
Investigation #2	HBT-03		

Investigation #3			
4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.			
a. For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?			
Investigation #1	HBT-03-CUTOFF	Yes	<input checked="" type="checkbox"/> No
IND#:			
Explain: There were no IND's submitted prior to the NDA submission. All studies were conducted under an IDE with CDRH as the primary reviewing agency			
Investigation #2	HBT-03	Yes	<input checked="" type="checkbox"/> No
IND#:			
Explain:			
Investigation #3		Yes	No
IND#:			
Explain:			
b. For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study? N/A			
Investigation #1		Yes	No
IND#:			
Explain:			
Investigation #2		Yes	No
IND#:			
Explain:			
Investigation #3		Yes	No
IND#:			
Explain:			
c. Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may			<input checked="" type="checkbox"/>

not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)	Yes	No ✓
If yes, explain:		



Signature of PM/CSO

Date:

12/6/99 ISI

Signature of Division Director

Date:

12/8/99 ISI

cc:

Original NDA

Division File

HFD-93 Mary Ann Holovac



The logo for Metabolic Solutions Inc. features the company name in a bold, sans-serif font. "Metabolic" is on the top line and "olutions" is on the bottom line, with "Inc." centered below "olutions". A circular arrow graphic surrounds the text, pointing clockwise.

**Metabolic
olutions**
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

Appendix E-2 - Claimed Exclusivity

Metabolic Solutions, Inc., believes that its new drug product known as Helicosol™ is entitled to a period of marketing exclusivity under provisions 314.108 (b) (4). Metabolic Solutions has met all the conditions of 314.108(b) (4). The company has conducted new clinical investigations that were essential to approval of the application and has submitted an application under section 505(b).

I certify that to the best of my knowledge each of the clinical investigations included in the attached application ((NDA 21-092) meets the definition of "new clinical investigations" set forth in 314.108(a).

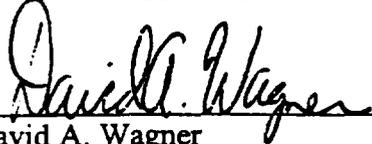
I have searched the literature for relevant studies and documents. I certify that to the best of my knowledge the following is a list of all published studies known to me through a literature search that are relevant to the conditions for which we are seeking approval.

1. Moulton-Barrett, R., G. Triadafilopoulous, R. Michener and D. Gologorsky. "Serum ¹³C-Bicarbonate in the Assessment of Gastric Helicobacter pylori Urease Activity." *Am.J.Gastroenterology*. 1993; 88:3, 369-374
2. Kim, M.J., R. Michener and G. Triadafilopoulous. "Serum ¹³C-Bicarbonate Assay for the Diagnosis of Gastric Helicobacter pylori Infection and Response to Treatment". *Gastroenterology*. 1997; 113:31-37

These listed studies are insufficient because 1) size of the studies was too small to demonstrate with any statistical power that the test worked, 2) the studies didn't demonstrate the safety of product, 3) the studies were conducted using non-GMP drugs and components, and 4) the pervious studies used two or more blood samples and the Metabolic Solutions test was developed using one sample. Therefore, it is my opinion that these published studies do not provide a sufficient basis for the approval of the conditions for which we are seeking approval.

Having meet the qualifications for exclusivity as outlined under 314.108(b) (4), and having demonstrated that compliance in this document, I would like to request that the FDA grant exclusivity.

I attest that this document is complete and true.



David A. Wagner
President, Metabolic Solutions, Inc.

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number: 21092 **Trade Name:** HELICOSOL (C13-UREA) 125MG

Supplement Number: **Generic Name:** C13-UREA

Supplement Type: **Dosage Form:** Powder For Reconstitution; Oral

Regulatory Action: AP **Proposed Indication:** The EZ-HBT is intended for use in the qualitative detection of 13CO2 in whole blood specimens, collected after the ingestion of 13C-urea.

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, No data was submitted for this indication, however, plans or ongoing studies exist for pediatric patients

What are the INTENDED Pediatric Age Groups for this submission?

 NeoNates (0-30 Days) X Children (25 months-12 Years)

 Infants (1-24 Months) X Adolescents (13-16 Years)

Label Adequacy Inadequate for ALL pediatric age groups

Formulation Status NO NEW FORMULATION is needed

Studies Needed STUDIES needed. Applicant in NEGOTIATIONS with FDA

Study Status Protocols are under discussion. Comment attached

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

Applicant requested deferral of pediatric requirement; deferral will be granted. One pediatric study has been submitted and approved; two additional protocols expected to be submitted in future.

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

Signature JS/

_____ 12/6/99 _____
Date



**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

Appendix E3

Debarment Certification

Metabolic Solutions, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this NDA Application 21-092.

Signed,



David A. Wagner, Ph.D.
President

3/17/99
Date

**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

Appendix E4

Field Copy Certification

I, David A. Wagner of Metabolic Solutions, Inc. certify that the field copy submitted to the United States Food and Drug Administration is an exact copy of the Chemistry Section (Technical Section Volume 2) contained in the Archival Copy of NDA Application 21-092.

Signed,



David A. Wagner, Ph.D.
President

3/17/99
Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service Food and Drug Administration CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS	Form Approved: OMB No. XXXX-XXXX Expiration Date: XX/XX/XX						
TO BE COMPLETED BY APPLICANT							
With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).							
Please mark the applicable checkbox.							
<input checked="" type="checkbox"/> (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).							
Clinical Investigators	<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%;">Dr. Dennis Riff</td> <td style="width: 50%;">Dr. Uma Murthy</td> </tr> <tr> <td>Dr. Philip Toskes</td> <td>Dr. Stephen Carpenter</td> </tr> <tr> <td>Dr. Alan Cutler</td> <td>Dr. Albert Cohen</td> </tr> </table>	Dr. Dennis Riff	Dr. Uma Murthy	Dr. Philip Toskes	Dr. Stephen Carpenter	Dr. Alan Cutler	Dr. Albert Cohen
Dr. Dennis Riff	Dr. Uma Murthy						
Dr. Philip Toskes	Dr. Stephen Carpenter						
Dr. Alan Cutler	Dr. Albert Cohen						
<input type="checkbox"/> (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).							
<input type="checkbox"/> (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.							
NAME David A. Wagner	TITLE President						
FIRM/ORGANIZATION Metabolic Solutions, Inc.							
SIGNATURE 	DATE 3/17/99						
Paperwork Reduction Act Statement							
An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:							
Department of Health and Human Services Food and Drug Administration 5600 Fishers Lane, Room 14C-03 Rockville, MD 20857							
Please DO NOT RETURN this form to this address.							

FORM FDA 3454 (10/98)

Control by Electronic Document Services/USDHHS: (201) 443-3434

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

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

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

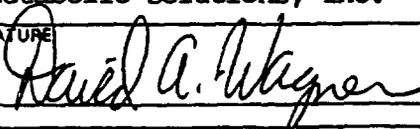
With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the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

Please mark the applicable checkbox.

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

Clinical Investigators	Dr. William Chey	Dr. Howard Schwartz
	Dr. Loren Laine	Dr. Ronald Pruitt
	Dr. Charles Barish	Dr. Barry Winston

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

NAME David A. Wagner	TITLE President
FIRM/ORGANIZATION Metabolic Solutions, Inc.	
SIGNATURE 	DATE 3/17/99

Paperwork Reduction Act Statement

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

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

Please DO NOT RETURN this form to this address.

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

Form Approved: OMB No. XXXX-XXXX
Expiration Date: XXXXXX

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

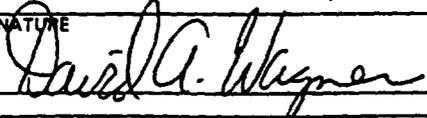
With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the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

Please mark the applicable checkbox.

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

Clinical Investigators	Dr. Miguel Zinny	

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

NAME David A. Wagner	TITLE President
FIRM/ORGANIZATION Metabolic Solutions, Inc.	
SIGNATURE 	DATE 3/17/99

Paperwork Reduction Act Statement

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

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

Please DO NOT RETURN this form to this address.

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE SENT: November 5, 1999

DUE DATE: N/A

OPDRA CONSULT #: 99-078

TO (Divisions):

Patricia Y. Love, MD
Director, Division of Medical Imaging and Radiopharmaceutical Drug Products
HFD-160

PRODUCT NAME:

Helicosol™ (¹³C-urea)

NDA #: 21-092

MANUFACTURER: Metabolic Solutions, Inc.

CASE REPORT NUMBER(S): N/A

SUMMARY:

In response to a consult from the Division of Medical Imaging and Radiopharmaceutical Drug Products (HFD-160), OPDRA conducted a review of the proposed proprietary name "Helicosol™" to determine the potential for confusion with approved proprietary and generic names as well as pending names.

OPDRA RECOMMENDATION:

OPDRA has no objections to the use of the proprietary name "Helicosol™".

/S/ _____ *11/3/99*
Jerry Phillips
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3246
Fax: (301) 827-5189

/S/ _____ *11/4/99*
Peter Honig, MD
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm 15B03
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: November 2, 1999
NDA# 21-092
NAME OF DRUG: Helicosol™ (¹³C-Urea)
NDA HOLDER: Metabolic Solutions, Inc.

I. INTRODUCTION:

This consult was written in response to a request from the Division of Oncology Drug Products (HFD-150) on October 28, 1999, to review the proposed proprietary drug name, Helicosol™ regarding potential name confusion with existing proprietary/generic drug names.

PRODUCT INFORMATION

Helicosol™, manufactured by Metabolic Solutions, Inc., was submitted under NDA 21-092. According to the project manager in HFD-150, CDER and CDRH are jointly reviewing this product. The package insert was the only labeling provided for review and comment. Helicosol™ is the diagnostic drug component of the Ez-HBT™ kit.

Helicosol™ is ¹³C-urea, a synthetic urea prepared as a lyophilized white powder for reconstitution. The powder is then reconstituted with sterile water for oral administration. Greater than or equal to 99% of the carbon molecules in the Helicosol drug component are in the form of ¹³C, a stable occurring isotope of carbon.

The Ez-HBT™ is intended for use in the qualitative detection of urease activity found associated with *Helicobacter pylori* (*H. pylori*) organisms colonizing the lining of the human stomach. The test kit is designed for use in adult subjects and should be administered under a physician's supervision. A qualified laboratory using Gas Isotope Ratio Mass Spectrometry or equivalent instrumentation must analyze the test samples.

The kit contains the following: Helicosol™ (¹³C-urea), Sterile Water, Straw, Ensure™, Vacutainer® tubes containing sodium heparin, Vacutainer® Brand Blood Collection System including needle and adapter, Alcohol wipe, Bandage, Tourniquet, and Gauze.

The patient is instructed to drink the Ensure™, wait five minutes and then administer the Helicosol™ solution. The patient ingests the oral dose of ¹³C-urea and the enzyme urease associated with gastric *H. pylori* converts urea into ¹³CO₂ and ammonia (NH₄⁺). The ¹³CO₂ is absorbed into the bloodstream and this results in an increase in the ratio of ¹³CO₂ in blood if *H. pylori* is present in the stomach. Analysis of the blood for increase levels of ¹³CO₂ is performed 30 minutes following consumption of the Helicosol™ solution. In the absence of gastric *H. pylori*, the test does not produce increased levels of ¹³CO₂ in the blood.

Currently there are six serological test kits commercially available that screen for *H. pylori* (Bio-Rad GAP, Helico-G, Premier, Pyloriset EIA-G, HM-CAP, and Oxoid Latex Kit). Information on administration of these tests and their contents were unavailable for review and thus it is difficult to determine if EZ-HBT™ is any *easier* to administer than these other tests.

II. RISK ASSESSMENT:

Due to the limited review time associated with this review, neither a written and verbal analysis of the name was not performed nor was it discussed in an OPDRA focus group. Therefore, in order to predict the potential for medication errors and to determine the degree of Confusion associated with the proposed name, "Helicosol™", with other approved and unapproved drug names, the medication error staff of OPDRA searched MICROMEDEX Healthcare Intranet Series, 1999, which includes the following published texts: DrugDex, Poisindex, Martindale, Emergindex, Reprodisk, Index Nominum, and Physicians' Desk Reference (1999). Additional publications utilized to search for potential sound-alike or look-alike names to approved drugs were the American Drug Index (43rd Edition), Drug Facts and Comparisons (Updated Monthly), the Electronic Orange Book, and US Patent and Trademark Office online database. OPDRA also searched several FDA databases for potential sound-alike or look-alike names to unapproved/approved drugs (Establishment Evaluation System (EES), Drug Product Reference File (DPR), Decision Support System (DSS) and the LNC database. These searches did not reveal any existing drug names that could cause confusion with "Helicosol™" and thus pose a significant safety risk. Lastly, the United States Adopted Names Council (USAN) Handbook, Fifth Edition, was searched to determine if the proprietary name "Helicosol™" utilized a USAN stem inappropriately. The proprietary name "Helicosol™" does not utilize any USAN stem.

RECOMMENDATIONS:

OPDRA does not object to the use of the proprietary name "Helicosol™".

If you have any questions concerning this review please contact Carol Holquist at 301-827-3244.

/S/

3/99

Carol Holquist, RPh
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur:

/S/

11/3/99

Jerry Phillips, RPh
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

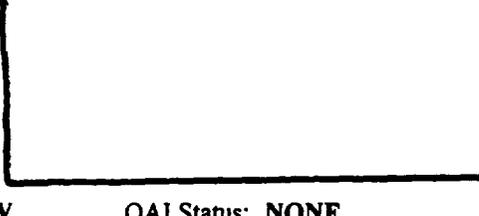
Application: NDA 21092/000	Priority: 5S	Org Code: 590
Stamp: 19-MAR-1999 Regulatory Due: 19-JAN-2000	Action Goal:	District Goal: 20-NOV-1999
Applicant: METABOLIC SOLUTIONS	Brand Name: HELICOSOL (C13-UREA) 125MG	
460 AMHERST ST	Established Name:	
NASHUA, NH 03063	Generic Name: C13-UREA	
	Dosage Form: FOX (FOR ORAL SOLUTION)	
	Strength: 125 MGS	
FDA Contacts: R. ANDERSON (HFD-590)	301-827-2478 , Project Manager	
R. HARAPANHALLI (HFD-160)	301-827-7510 , Review Chemist	
E. LEUTZINGER (HFD-160)	301-827-7510 , Team Leader	

Overall Recommendation:

ACCEPTABLE on 23-NOV-1999 by S. FERGUSON(HFD-324)301-827-0062

Establishment:		DMF No:	
		AADA No:	
Profile: CTL	OAI Status: NONE	Responsibilities: FINISHED DOSAGE RELEASE	
Last Milestone: OC RECOMMENDATION		TESTER	
Milestone Date: 14-APR-1999			
Decision: ACCEPTABLE			
Reason: BASED ON PROFILE			

Establishment:		DMF No:	
		AADA No:	
Profile: CSN	OAI Status: NONE	Responsibilities: DRUG SUBSTANCE	
Last Milestone: OC RECOMMENDATION		MANUFACTURER	
Milestone Date: 23-NOV-1999			
Decision: ACCEPTABLE			
Reason: DISTRICT RECOMMENDATION			

Establishment:		DMF No:	
		AADA No:	
Profile: POW	OAI Status: NONE	Responsibilities: FINISHED DOSAGE	
Last Milestone: OC RECOMMENDATION		MANUFACTURER	
Milestone Date: 09-NOV-1999			
Decision: ACCEPTABLE			

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Reason: **DISTRICT RECOMMENDATION**

Establishment: **1223869**
METABOLIC SOLUTIONS INC
7 HENRY CLAY DRIVE
MERRIMACK, NH 03054

DMF No:
AADA No:

Profile: **POW** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **18-NOV-1999**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **FINISHED DOSAGE**
MANUFACTURER

**APPEARS THIS WAY
ON ORIGINAL**

**APPEARS THIS WAY
ON ORIGINAL**

Team Leader's Memorandum

To: NDA 21-092
From: Robert Hopkins MD, MPH & TM
Re: Helicosol NDA 21-092
Date: December 17, 1999

The purpose of this memorandum is to review the financial information submitted by the sponsor to assure that steps have been taken to minimize the potential for bias. There were 13 investigators who were listed on the form 3454 financial disclosure form. The sponsor certified that none of these investigators received significant payments or entered into any financial arrangement with the sponsor as outlined on this form.

The following list outlines all investigators participating in clinical studies that supported this application.

Study HBT-01

Phillip Toskes
Alan Cutler

Study HBT-02

William Chey
Phillip Toskes
Loren Laine
Uma Murthy
Stephen Carpenter

Study HBT-03

Loren Laine
William Chey
Howard Schwartz
Barry Winston
Dennis Riff
Ronald Pruitt
Charles Barish

Study HBT-01 Amend 1

Albert Cohen

Study HBT-04

Miguel Zinny

All these investigators were listed on FDA form 3454 submitted by the sponsor and signed by Dr. David A Wagner, President, Metabolic Solutions Inc. Therefore, the Division acknowledges that steps have been taken to minimize the potential for bias. In addition, I concur with the clinical/statistical review authored by Drs. Joette Meyer and Karen Higgins.

/S/

12/17/99

Robert J. Hopkins MD, MPH & TM
Medical Team Leader

Concurrence:

Mark Goldberger MD, MPH WJG
Division Director

cc:

HFD-590/Div File/NDA 21-091
HFD-590/TLMO/HopkinsR
HFD-590/ClinPharm/MeyerJ
HFD-590/PM/FritschJ

Meeting Memorandum

Date: July 15, 1999

Subject: Metabolic Solutions, Inc. Ez-HBT™ Helicobacter Blood Test

Participants:

CDRH: Woody R. Dubois, Ph.D., Branch Chief
Pandur Soprey, Ph.D.
Freddie M. Poole, Team Leader

CDER: Robin Anderson, RN, MBA, Project Manager
Mark Goldberger, M.D., Division Director
Robert Hopkins, M.D., Medical Team Leader
Joette Meyer, Pharm.D., Clinical Pharmacology and
Biopharmaceutics Reviewer
Karen Higgins, Ph.D. Biostatistician
Nancy P. Silliman, Ph.D., Biostatistical Team Leader
Steve Hundley, Ph.D., Pharmacologist
HFD-160:
Ravi Harapanhalli, Ph.D., Chemist
Eldon Leutzinger, Ph.D., Chemistry Team Leader

The meeting was convened to discuss the product labeling for Metabolic Solutions EZ-HBT Helicobacter Blood Test. Robin Anderson, the Project Manager, distributed copies of CDER's proposed labeling revisions. Dr. Leutzinger asked CDRH for the status and timeframe of the review. Dr. Dubois explained that the submission was on hold, however the sponsor had informed us that the amendment to the submission would be arriving shortly. We would then have 90 days in which to complete the submission.

Dr. Harapanhalli presented his preliminary review of the product labeling. He believes that there should be additional information on the Ensure™ given to the patient, since it is used in conjunction with the drug. There was a short discussion about the necessity of this information, and it was finally agreed that it would be useful. Dr. Harapanhalli also presented a uniform storage statement that should be added to the package insert, vial and carton labels. He then informed the group that the Manufacturing Site inspection was not completed. One site was completed and found satisfactory, however there were three more sites to be inspected. (N.B. Metabolic Solution was not the primary manufacturer. [redacted] assembled the kit, [redacted] manufactured the drug component, and [redacted] manufactured the lyophilized powder formulation.)

Joette Meyer then presented the clinical/statistical review. CDER stated that the cutoff point in the pivotal study (HBT-03) was refined from ~17.0 to ~17.5 delta per ml and an indeterminate zone of +/- delta per ml was created. By doing so, the sponsor improved the test sensitivity. CDER suggested that the sponsor might need to conduct studies to validate the new cutoff point and indeterminate zone post approval. Another approach was also proposed by CDER to validate the sponsor's results with the available data. By randomly separating the data into two independent groups, data from one group could be used to determine a cutoff and then data from the other group could be used to determine the performance characteristics using the new cutoff. CDER will work on performing these simulations.

The graph in the package insert demonstrating the cutoff point is not accurate. About 20 false results (9 false positive results and 11 false negatives) were not included. The sponsor should explain why they were excluded.

Additionally, in the study to demonstrate the effect of blood collection time on the assay, there seemed to be an increase in Ez-HBT values as the sample time increases for the positive samples. However, there was no increase in time for the subjects, who were negative at 30 minutes. Suggest asking the sponsor why 30 minutes was selected instead of 60 or even 45 minutes.

The Stability Data conducted to demonstrate the effects of shipping by air showed differences greater than the size of the indeterminate zone ($\delta 1.0$). Of the twenty patients evaluated, eleven had values > 1.0 , one has high as 2.3. These differences are significant and the sponsor should address them. Also information on the integrity of the containers during shipping should be provided.

Labeling Review: Enrolled in the Clinical trials were three patients who had received a proton pump inhibitor (PPI) within 7 days prior to the Ez-HBT test. This was listed as an exclusion criterion. Another patient was included who had a history of gastroparesis, which was also an exclusion criterion. (These patients were excluded from CDER's sensitivity and specificity analyses). The sponsor should explain why they were not excluded.

In the Performance Characteristics section, Tables 1 and 2 should be revised to include an Indeterminate Zone and to remove the 4 patients who had received a PPI.

False Positive and False Negative results: The sponsor should be asked what percent of the False Positive and False Negatives were due to user inexperience or performed incorrectly. (N.B. 55% of the false results came from among the first samples done at any site.) A rewording of the labeling may be necessary if $> 50\%$ of the FN and FP were caused by inexperience.

CDER also recommended other revisions (see attached package insert) to the package insert to clarify instructions for use and to be consistent with the package insert.

CDRH proposed a modification to the intended use to clarify that the assay is not a "breath" collection test but requires "whole blood" collection. The labeling could more appropriately state "The Ez-HBT™ is intended for use in the qualitative detection of $^{13}\text{CO}_2$ in whole blood specimens, collected after the ingestion of ^{13}C -urea. Urease activity is associated with *Helicobacter pylori* organisms found in the lining of the human stomach. The device is indicated for use to aid in the diagnosis of *H. pylori* infection in symptomatic adult subjects 18 years of age and older.

CDER agreed to complete their review by the second week in August. A teleconference with the sponsor to address the labeling issues will be scheduled soon after.

Post Meeting Corrigenda:

A telecon was subsequently scheduled with Metabolic Solutions and CDRH/CDER for August 19, 1999.

AUG 19 1999

MEMORANDUM OF TELECON

DATE: June 24, 1999

APPLICATION NUMBER: NDA 20-916; Helicosol Blood Test for *H. pylori*

BETWEEN:

Name: Dr. David Wagner
Phone: (603) 598-6960
Representing: Metabolic Solutions, Inc.

AND

Name: Robin Anderson, Project Manager
Laurie Bernato, Project Manager
Dr. Robert Hopkins, Medical Team Leader
Division of Special Pathogen and Immunologic Drug Products, HFD-590

SUBJECT: Pediatric Study Plans for Helicosol

DISCUSSION:

- Dr. Hopkins discussed the recent final Pediatric Rule as it relates to NDAs. FDA may waive the rule in certain instances if the sponsor can provide reasonable justification for not pursuing pediatric studies. Dr. Wagner stated that his company does plan to do pediatric studies, but would prefer to market the product to adults first and then pursue the pediatric population.

Post Meeting Corrigenda:

The next day Dr. Hopkins requested that Ms. Anderson call Dr. Wagner and request that he submit proposed pediatric protocols for review before implementing them. Dr. Wagner stated that since the action for this NDA probably would be at the end of this summer, the phase one study would be scheduled to begin in September, 1999. He agreed to submit that protocol for review ASAP.

/s/

Robin Anderson
Project Manager