Purchasing and Property Services
AOC 200
4202 East Fowler Avenue
Tampa, Florida 33620
(813) 974-2481

Web Address: http://usfweb.usf.edu/purchasing/purch2.htm

March 11, 2011

Invitation to Negotiate No.	11-15-MH
Entitled:	Type 1 Diabetes TrialNet Central Pharmacy Services
Opening Date:	April 15, 2011 at 3:00pm

Addendum No. 1

Please review the following changes/additions to Invitation to Negotiate (ITN) No. 11-15-MH to be addressed in submitted proposals:

Documents can be found at this link: **Current Bids Available**

If you have any questions, please address them to Michael Hernandez: mahernandez@admin.usf.edu

ATTENTION ALL POTENTIAL BIDDER'S, REGARDING ITN 11-15-MH.

Vendor Questions Regarding ITN 11-15-MH
Type 1 Diabetes TrialNet Central Pharmacy Services

1. Q. Regarding exhibit A IND 76419; does the University of South Florida have a supply of Insulin crystals that are to be used to produce the indicated capsules?
   A. Yes, Eli Lilly supplies the insulin crystals and ships directly to central pharmacy.

2. Q. Will the Zinc Insulin Human Crystals that Eli Lilly provides be supplied to the proposing vendor, or will vendor need to include the cost of this material in their proposal?
   A. The Zinc Insulin Human Crystals will be supplied to the proposing vendor at no cost. TrialNet has order forms in place to facilitate this process.

3. Q. If the vendors are expected to obtain Zinc Insulin Crystals from Eli Lilly does USF have a contact person with Eli Lilly?
   A. Yes. The specific contact information can be provided.

4. Q. Do you have a source for the Microsolle material specified in the formulation?
   A. Information regarding the source for the Microsolle can be provided.

5. Q. What is the grade of Avicel that was utilized?
   A. Information regarding the grade of Avicel can be provided.

6. Q. Can USF provide copied of previous manufacturing batch records?
   A. Yes. This information can be provided.

7. Q. Does your business have to be located in the state of Florida to Bid on ITN 11-15-MH Type 1 Diabetes central Pharmacy Services?
   A. No.

8. Q. Will investigational studies involve compounding of IV (parenteral) medications?
   A. No. Current TrialNet studies which involve IV administration(s) of the investigational drug product do not require compounding. The local pharmacists at the TrialNet sites are responsible for preparing (mixing, diluting, etc.) the investigational drug product according to the manufacturer's specifications prior to administration.

9. Q. Are there manufacturing instructions for the preparation of the capsuled?
   A. See specifications in document below " Insulin Human Bulk Drug Substance" (Specifications)

10. Q. What are the finished product specifications?
    A. See specifications in document below " Insulin Human Bulk Drug Substance" (Specifications)

11. Q. Are test methods available to perform QC testing on the finished capsules?
    A. See specifications in document below " Insulin Human Bulk Drug Substance" (Specifications)

Note: **Please note receipt of this addendum by signing and returning with your proposal response.**

_____

Authorized Signature & Date

_____

Print Name

_____

Company Name

INSULIN HUMAN BULK DRUG SUBSTANCE

SPECIFICATIONS

Client Name
Address

Reference
Contact:

Test		Specification
1.	*Physical Examination*	*White to off-white powder*
2.	*Identification*	
	HPLC	*Conforms with Reference Standard*
	Peptide Mapping	*Meets USP Specifications*
3.	*Bioidentity*	*Meets USP Specifications*
4.	*Loss on drying, USP <731>*	*NMT 10%*
5.	*Zinc*	*NMT 1.0% on dried basis*
6.	*Assay,(HPLC)*	*NLT 27 Units/mg (on dried basis)*
7.	*Related Compounds, USP*	*NMT 2.0%*
8.	*Limit of High Molecular Weight Proteins*	*NMT 1.0%*
9.	*Bacterial Endotoxins Test, USP <85>*	*NMT 10 EU/mg*
10.	*Microbial Limits, USP<61>*	*NMT 300 cfu/g*

Comment: The specifications listed above are as specified in the USP for Insulin Human.

www.lilly.com

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285
U.S.A.

Phone 317 276 2000

CERTIFICATE OF ANALYSIS
QA307X – Zinc-Insulin Crystals Human: Proinsulin Derived (Recombinant DNA Origin)

Lot Number: 032LX5 | **Manufacture Date:** MAY-02-2005 | **Release Date:** JUL-20-2005
US Reevaluation Due: MAR-23-2007
Country: United States | **Register Number:** N/A | **PO Number:** N/A

Comments and Restrictions: None

Assay	Pharmacopoeia References	Result	Method	Specification
Potency:				
Assay		98.9 %	B03025	95.0–105.0% on a dried basis by HPLC
Potency	USP	28.55 U/mg	B03025	NLT 27.5 U/mg on a dried basis by HPLC
Potency		26.31 U/mg	B03025	On an "as is" basis
Impurities:				
A-21 Desamido Insulin	USP	0.26 %	B01962	NMT 2.00% by HPLC
Desthreonine (B30) Insulin		0.1 %	A00137	NMT 1.0% by HPLC
Total Other Insulin-Related Substances	USP	0.58 %	B01962	NMT 2.00% by HPLC
High Molecular Weight Proteins	USP/Ph. Eur.	<0.06 %	B03622	NMT 1.00% by size exclusion HPLC
Human Proinsulin		<1 ppm	B05385	NMT 10 ppm by ELISA
Immunoreactive *E. coli* Polypeptides		<2 ppm	B04738	NMT 10 ppm by ELISA
Other tests:				
Loss on Drying	USP/Ph. Eur./JP	7.8 %	A00031	NMT 10.0%
Zinc	USP/Ph. Eur.	0.410 %	A00030	0.30-0.60% on a dried basis
Sulfated Ash	BP	0.54 %	B00953	NMT 2.0%
Bacterial Endotoxins	USP/JP	<2.5000 EU/mg	A13454	NMT 10 EU/mg
Microbial Limit	USP	<3 org/g	B01812	NMT 100 org/g
Identity tests:				
UV Absorbance	Ph. Eur.	10.36	A00115	10.0-11.0 AU @ 276 nm
Physical Appearance	USP/Ph. Eur.	Pass	A02637	It is a white to off-white powder visually
Identification	USP/Ph. Eur.	Pass	B03025	The Retention time of the main peak in the HPLC potency assay compares favorably with that of the reference standard
Fingerprint Analysis (Peptide Map)	USP/Ph. Eur.	Pass	B06093	Conforms to reference standard by HPLC
Bioidentity	USP	Pass	A13837	Passes test

Prepared by: JoEllen Hamilton Date: JUL-07-2006

Verified by: Date JUL 07 2006

Zinc-Insulin Crystals Human

Effective Date: 27-Sep-2003

Eli Lilly and Company
Material Safety Data Sheet

Section 1 - Chemical Product and Company

Manufacturer:
Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

Manufacturer's Emergency Phone:
1-317-276-2000
CHEMTREC:
1-800-424-9300 (North America)
1-703-527-3887 (International)

Common Name: Zinc-Insulin Crystals Human

CAS Number(s): 11061-68-0
Chemical Name: Insulin (human)
Chemical Family: Polypeptide hormone
Chemical Formula: C1542 H2298 N390 O462 S36 Zn2
Molecular Weight: 34976.93
Synonym(s): Zinc-insulin crystals spray dried; Insulin; Zinc insulin crystals human; Human insulin; BHI; Biosynthetic human insulin; Insulin zinc crystals - proinsulin derived; ZIC-human
Trademarks(s): Humulin
Lilly Serial Number(s): 041001
Lilly Item Code(s): ID4023; ID4030; ID4034; QA256Q; QA274G; QA292A; QA307X; QA333W; QA353Q; QA461K; QD370E; QD482Q; QS2213; QS2442; QS2450; QS2499; QS4442; QS4450; QS4498; QS4499

See attached glossary for abbreviations.

Section 2 - Composition / Information on Ingredients

Ingredient	CAS
Zinc-Insulin Crystals Human	11061-68-0

Exposure Guidelines:
Insulin crystals - LEG 120 micrograms/m3 TWA (respirable) for 12 hours, 600 micrograms/m3 TWA (respirable) for 15 minutes STEG.

Section 3 - Hazards Identification

Appearance: White to off-white crystalline powder
Physical State: Solid

Odor: Odorless

Emergency Overview

Emergency Overview Effective Date: 23-Oct-1999

Lilly Laboratory Labeling Codes:
Health 0 **Fire** 1 **Reactivity** 0

Primary Physical and Health Hazards: Hormonal Effects.

Caution Statement: Effects of exposure to Zinc-Insulin Crystals Human may include decreased blood sugar.

Routes of Entry: Inhalation and skin contact.

Effects of Overexposure: Symptoms of faintness, shakiness, and weakness have been reported, possibly due to blood sugar lowering effects caused by inhalation of insulin powder. Insulin is a naturally occurring hormone. Symptoms typically associated with low blood sugar include shakiness, sweating, fatigue, hunger, irritability, confusion, and rapid heartbeat. Not expected to be active orally.

Medical Conditions Aggravated by Exposure: Hypersensitivity to insulin.

Carcinogenicity:
Zinc-insulin crystals human - Not listed by IARC, NTP, ACGIH, or OSHA. One-year subcutaneous injection studies with insulin, lispro demonstrated no evidence of carcinogenicity in rats.

Section 4 - First Aid Measures

Eyes: Flush eyes with plenty of water. Get medical attention.

Skin: Remove contaminated clothing and clean before reuse. Wash all exposed areas of skin with plenty of soap and water. Get medical attention if irritation develops.

Inhalation: Move individual to fresh air. Get medical attention if breathing difficulty occurs. If not breathing, provide artificial respiration assistance (mouth-to-mouth) and call a physician immediately.

Ingestion: Call a physician or poison control center. No first aid procedures are normally required.

Section 5 - Fire Fighting Measures

Flash Point: No applicable information found
UEL: No applicable information found

LEL: No applicable information found

Extinguishing Media: Use water, carbon dioxide, dry chemical, foam, or Halon.

Unusual Fire and Explosion Hazards: As a finely divided material, may form dust mixtures in air which could explode if subjected to an ignition source.

Hazardous Combustion Products: May emit toxic fumes when exposed to heat or fire.

Section 6 - Accidental Release Measures

Spills: Vacuum material with appropriate dust collection filter in place. Be aware of potential for dust explosion when using electrical equipment. If vacuum is not available, lightly mist material and remove by sweeping or wet wiping. Wear protective equipment, including eye protection, to avoid exposure (see Section 8 for specific handling precautions).

Section 7 - Handling and Storage

Storage Conditions: Freezer: -10 to -25 C (14 to -13 F).

Section 8 - Exposure Controls / Personal Protection

See Section 2 for Exposure Guideline information.

Respiratory Protection: Use an approved respirator.

Eye Protection: Safety glasses.

Ventilation: Laboratory fume hood or local exhaust ventilation.

Other Protective Equipment: Chemical-resistant gloves and body covering to minimize skin contact. If handled in a ventilated enclosure, as in a laboratory setting, respirator and goggles or face shield may not be required. Safety glasses are always required.

Additional Exposure Precautions: During blending and sieving operations, dust goggles and dust respirator or Bullard hood are recommended.

Section 9 - Physical and Chemical Properties

Appearance: White to off-white crystalline powder
Odor: Odorless
Boiling Point: Not applicable
Melting Point: Decomposes before melting
Density: No applicable information found
pH: 7.1-7.4
Evaporation Rate: Not applicable

Water Solubility: Slightly soluble
Vapor Density: Not applicable
Vapor Pressure: Not applicable

Section 10 - Stability and Reactivity

Stability: Stable at normal temperatures and pressures.

Incompatibility: May react with strong oxidizing agents (e.g., peroxides, permanganates, nitric acid, etc.).

Hazardous Decomposition: May emit toxic fumes when heated to decomposition.

Hazardous Polymerization: Will not occur.

Section 11 - Toxicological Information

Acute Exposure

The toxicity data for the material or related material(s) are presented.

Oral: No applicable information found.

Skin: No applicable information found.

Inhalation: No applicable information found.

Intravenous:
Insulin, lispro crystals - Rat, 10 units/kg, no deaths or toxicity.
Dog, 0.1 units/kg, no deaths, decreased blood glucose values.

Subcutaneous:
Insulin, lispro crystals - Rat, 10 units/kg, no deaths or toxicity.
Dog, 2 units/kg, no deaths or toxicity.

Skin Contact: No applicable information found.

Eye Contact: No applicable information found.

Chronic Exposure

The toxicity data for the material or related material(s) are presented.

Target Organ Effects:
Insulin - Hormonal effects (decreased blood sugar).

Reproduction:
Insulin - Mixed results reported in animal studies. Effects were attributed to hypoglycemia. Insulin itself is not considered a reproduction hazard.

Sensitization:
Insulin, lispro crystals - Rhesus monkeys, extremely weak immunogenic potential.

Mutagenicity:
Zinc-insulin crystals human - Not mutagenic in bacterial or mammalian cells.

Section 12 - Ecological Information

No applicable ecological information found.

Section 13 - Disposal Considerations

Waste Disposal: Dispose of any cleanup materials and waste residue according to all applicable laws and regulations.

Section 14 - Transport Information

Regulatory Organizations:

DOT: Not Regulated

ICAO/IATA: Not Regulated

IMO: Not Regulated

Section 15 - Regulatory Information

Below is selected regulatory information chosen primarily for possible Eli Lilly and Company usage. This section is not a complete analysis or reference to all applicable regulatory information. Please consider all applicable laws and regulations for your country/state.

U.S. Regulations

TSCA - No
CERCLA - Not on this list
SARA 302 - Not on this list
SARA 313 - Not on this list
OSHA Substance Specific - No

EU Regulations

EC Classification
Not assigned an overall EC classification.

Section 16 - Other Information

MSDS Sections Revised: Sections 1, 2, 3, and 11.

As of the date of issuance, we are providing available information relevant to the handling of this material in the workplace. All information contained herein is offered with the good faith belief that it is accurate. THIS MATERIAL SAFETY DATA SHEET SHALL NOT BE DEEMED TO CREATE ANY WARRANTY OF ANY KIND (INCLUDING WARRANTY OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE). In the event of an adverse incident associated with this material, this safety data sheet is not intended to be a substitute for consultation with appropriately trained personnel. Nor is this safety data sheet intended to be a substitute for product literature which may accompany the finished product.

For additional information contact:
Eli Lilly and Company
Hazard Communication
317-651-9533

GLOSSARY:

ACGIH = American Conference of Governmental Industrial Hygienists
AIHA = American Industrial Hygiene Association
BEI = Biological Exposure Index
CAS Number = Chemical Abstract Service Registry Number
CERCLA = Comprehensive Environmental Response Compensation and Liability Act (of 1980)
CHAN = Chemical Hazard Alert Notice
CHEMTREC = Chemical Transportation Emergency Center
DOT = Department of Transportation
EC = European Community
EINECS = European Inventory of Existing Chemical Substances
ELINCS = European List of New Chemical Substances
EPA = Environmental Protection Agency
HEPA = High Efficiency Particulate Air (Filter)
IARC = International Agency for Research on Cancer
ICAO/IATA = International Civil Aviation Organization/International Air Transport Association
IEG = Lilly Interim Exposure Guideline
IMO = International Maritime Organization
Kow = Octanol/Water Partition Coefficient
LEG = Lilly Exposure Guideline
LEL = Lower Explosive Limit
MSDS = Material Safety Data Sheet
MSHA = Mine Safety and Health Administration
NA = Not Applicable, except in Section 14 where NA = North America
NADA = New Animal Drug Application
NAIF = No Applicable Information Found
NCI = National Cancer Institute
NIOSH = National Institute for Occupational Safety and Health
NOS = Not Otherwise Specified
NTP = National Toxicology Program

OSHA = Occupational Safety and Health Administration
PEL = Permissible Exposure Limit (OSHA)
RCRA = Resource Conservation and Recovery Act
RQ = Reportable Quantity
RTECS = Registry of Toxic Effects of Chemical Substances
SARA = Superfund Amendments and Reauthorization Act
STEG = Lilly Short Term Exposure Guideline
STEL = Short Term Exposure Limit
TLV = Threshold Limit Value (ACGIH)
TPQ = Threshold Planning Quantity
TSCA = Toxic Substances Control Act
TWA = Time Weighted Average/8 Hours Unless Otherwise Noted
UEL = Upper Explosive Limit
UN = United Nations
WEEL = Workplace Environmental Exposure Level (AIHA)

7.2 Drug Products

The following are the two drug products that will be used in the proposed study.

Insulin Human 7.5 mg Capsules, 190 Caps/Bottle

Placebo for Insulin Human 7.5 mg Capsules, 190 Caps/Bottle

The manufacturing process for each of the study products will be provided in detail along with copies of pertinent manufacturing batch records when available as Amendment to this IND.

7.2.1 **Insulin Human 7.5 mg Capsules**

7.2.1.1 Components

Insulin Human
Microsolle®
ProSolv®
CAB-O-SIL M5®
Avicel®
Hard Gelatine Capsule, #2

7.2.1.2 Composition

The following is the composition of Insulin Human 7.5 mg Capsules.

Insulin Human
Microsolle®
ProSolv®
CAB-O-SIL M5®
Avicel®

Fill Weight 200.0 mg

7.2.1.3 Specification and Analytical Methods for Inactive Components

The following are the inactive ingredients used in the manufacture of Insulin 7.5 mg Capsules. All these ingredients are of compendial grade. The specifications are clearly outlined in respective monographs in USP/NF.

Micosolle®
ProSolv®
CAB-O-SIL M5®
Avicel®

Certificate of Analysis for the actual lots to be used in the production process will be provided as Amendment to this IND when available.

7.2.1.3.1 Micosolle®

Manufacturer: Biomicotec,
Torrance, CA

Certificate of Analysis from the manufacturer for the exact lot used in the manufacture will be provided at a later date along with the completed Batch Record.

7.2.1.3.2 ProSolv (Silicified Microcrystalline Cellulose)

Manufacturer: JRS Pharma LP
2981 Route 22, Suite #1
Patterson, NY 12563-2359

Specification sheet of ProSolv HD90 from the manufacturer is provided in the following page.

Certificate of Analysis from the manufacturer for the exact lot used in the manufacture will be provided at a later date along with the completed Batch Record.

7.2.1.3.3 Avicel® (Microcrystalline Cellulose, NF)

Manufacturer FMC Corporation, Inc.
1735 Market Street
Philadelphia, PA 19103

Microcrystalline Cellulose is a subject of NF.

Certificate of Analysis from the manufacturer for the exact lot used in the manufacture will be provided at a later date along with the completed Batch Record.

7.2.1.3.4 CAB-O-SIL M5 (Colloidal Silicone Dioxide, NF)

Manufacturer: Cabot Corporation
CAB-O-SIL Division
700 E. U.S. Highway 36
Tuscola, IL 61953-9643

Colloidal Silicone Dioxide is a subject of NF.

Certificate of Analysis from the manufacturer for the exact lot used in the manufacture will be provided at a later date along with the completed Batch Record.

7.2.1.3.5 Hard Gelatin Capsule, #2 (Red)

Manufacturer: Capsugel
101 A Milledge Road
Greenville, SC 29646

Gelatin is a subject of NF.

Certificate of Analysis from the manufacturer for the exact lot used in the manufacture will be provided at a later date along with the completed Batch Record.

7.2.1.4 Product Manufacturer

7.2.1.5 Methods of Manufacturing and Packaging

7.2.1.5.1 Manufacturing Operations

All manufacturing steps are detailed in the Manufacturing Batch Record. Completed records for specific lots to be used in the study will be provided when available as Amendment to this IND.

7.2.1.5.2 Batch Record

Copies of the actual completed production batch records will be provided as Amendment to the IND when available.

7.2.1.5.3 Reprocessing Operations

TrialNet, NIDDK has no intention to reprocess any of the study products used in this study.

7.2.1.6 Specifications and Analytical Methods for the Drug Product.

The specifications and analytical test procedures to be used for the finished product testing of *Insulin Human Capsules, 7.5 mg* are provided below.

Finished product release testing will be performed by the following contract laboratory.

The Finished Product Release Testing will include the following tests:

Physical Examination
Identification, HPLC
Assay, on dry basis (HPLC)
Water Determination, USP <921>
Uniformity of Dosage Units (CU), USP <905>
Disintegration, USP <701>
Dissolution Testing, USP <711>
Bacterial Endotoxins Test, USP <85>
Microbial Limits, USP<61>

Product Specifications are provided in the following page.

7.2.1.7 Product Stability

In order to ensure the integrity of the study product, the TrialNet, NIDDK proposes to conduct ongoing stability study of the study products following ICH guidelines at 40°C + 75% RH (accelerated) with test stations 1, 2, 3, 4, 5, and 6 months and at 25°C + 60% RH (long-term) with test stations at 0, 3, 6, 12, 18, 24, and 36 months

Interim stability reports of will be provided to the Agency in the IND Annual Reports.

The stability testing at each test station will include

Physical Examination
Assay (Stability Indicating), HPLC
Water Determination, USP
Disintegration Testing, USP
Dissolution, USP

7.0 CHEMISTRY, MANUFACTURING AND CONTROLS

7.1 Drug Substance

Insulin Human, USP

Please refer to Eli Lilly and Company's IND 17,805; Serial Number 204 for details of Chemistry Manufacturing and Controls information pertaining to oral insulin bulk drug substance. Reference Authorization letter dated October 19, 2006 is provided in the following page.

Specifications of the *Insulin Human* as indicated in the USP Monograph were provided in the following page.

Certificate of Analysis for *Insulin Human* from the manufacturer is provided in the following page.

INSULIN HUMAN CAPSULES, 7.5 mg

FINISHED PRODUCT RELEASE SPECIFICATIONS

Client Name
Address

Test		Specification
1.	*Physical Examination*	*Size #2 Red hard gelatine Capsule containing White to off-white crystalline powder*
2.	*Identification*	
	HPLC	*Conforms with Reference Standard*
3.	*Assay, on dry basis (HPLC)*	*90-110% Label claim*
4.	*Water Determination, USP <921>*	*For Information Only*
5.	*Uniformity of Dosage Units (CU), USP <905>*	*Meets USP Specifications*
6.	*Disintegration, USP <701>*	*NLT 30 minutes*
7.	*Dissolution Testing, USP <711>*	*To be determined*
8.	*Bacterial Endotoxins Test, USP <85>*	*NMT 100 EU /Capsule*
9.	*Microbial Limits, USP<61>*	*NMT 300 cfu/g*

Comment: The specifications listed above are tentative and are based upon the experimental data obtained from initial lots of drug product manufactured. These specifications will be reviewed and revised upon completion of stability studies on clinical lots.

7.2.2 **Placebo for Oral Insulin 7.5 mg Capsules**

In order to blind the study products, TrialNet, NIDDK proposes to manufacture placebo Capsules that looks identical to *Insulin 7.5 mg Capsules* referred in section 7.1.2.

7.2.2.1 Components

Microsolle®
ProSolv®
CAB-O-SIL M5®
Avicel®
Hard Gelatine Capsule, #2

7.2.2.2 Composition

The following is the composition of Placebo for Insulin 7.5 mg Capsule.

Microsolle®	
ProSolv®	
CAB-O-SIL M5®	
Avicel®	
Fill Weight	200.0 mg

7.2.2.3 Specification and Analytical Methods for Inactive Components

Specifications and Analytical Methods for the inactive components are similar to information provided in section 7.2.1.3.

7.2.2.4 Product Manufacturer

7.2.2.5 Methods of Manufacturing and Packaging

7.2.2.5.1 Manufacturing Operations

All manufacturing steps are detailed in the Manufacturing Batch Record. Completed records for specific lots to be used in the study will be provided when available as Amendment to this IND.

7.2.2.5.2 Batch Record

Copies of the actual completed production batch records will be provided as Amendment to the IND when available.

7.2.2.5.3 Reprocessing Operations

TrialNet, NIDDK has no intention to reprocess any of the study products used in this study.

7.2.2.6 Specifications and Analytical Methods for the Drug Product.

The specifications and analytical test procedures to be used for the finished product testing of *Placebo for Insulin Human Capsules, 7.5 mg* are provided below.

Finished product release testing will be performed by the following contract laboratory.

The Finished Product Release Testing will include the following tests:

Physical Examination
Identification, HPLC
Water Determination, USP <921>
Uniformity of Dosage Units (WV), USP <905>
Disintegration, USP <701>
Bacterial Endotoxins Test, USP <85>
Microbial Limits, USP<61>

7.2.2.7 Product Stability

In order to ensure the integrity of the study product, the TrialNet, NIDDK proposes to conduct ongoing stability study of the study products following ICH guidelines at 40°C + 75% RH (accelerated) with test stations 1, 2, 3, 4, 5, and 6 months and at 25°C + 60% RH (long-term) with test stations at 0, 3, 6, 12, 18, 24, and 36 months

Interim stability reports of will be provided to the Agency in the IND Annual Reports.

7.3 Product Packaging

7.3.1 Bulk Packaging

The following study products are packaged bulk in double polyethylene lined containers as referenced in respective Master Production Batch Records.

Insulin Human 7.5 mg Capsules
Placebo Insulin Human 7.5 mg Capsule

7.3.2 Clinical Packaging

In order to maintain the patient compliance and blinding the study products are packaged in 200 cc HDPE Bottles 190 Capsules per bottle. The details of container closure system are provided in the following pages

7.3.2.1 Container Closure System

HDPE Bottles, 38-400 Round, 200 cc and 38-400 Caps, HS35-F217

HDPE Bottles Manufacturer:

Tim Plastics
97 N. Leslie Road, P.O. Box V
North East, MD 29101

Tel : (410) 287-6944
Fax : (410) 287-6945

Specifications and lot specific Certificate of Analysis will be provided along with the completed batch record.

Caps Manufacturer

Mold-Rite Plastics, Inc.
1 Plant Street, P.O. Box 160
Plattsburgh, NY 12901

Tel : (518) 561-1812
Fax : (803) 714-0670

Specifications and lot specific Certificate of Analysis will be provided along with the completed batch record.

PACKAGING COMPONENTS SPECIFICATIONS

Description: **Bottle, 38-400, 200 cc (White) - Tim Plastics** ID #: **EP-0006**

Parameter	Specification	Method
Outer Diameter (inches)	2.1870±0.031	Measure
Total Height (inches)	4.550±0.047	Measure
Mouth Diameter (inches)	1.464±0.015	Measure
Weight (grams)	19.5±2.0	Weight
Volume (mL)	225±5.0	Measure
Color	White	Visual
Shape	Round	Visual
Material	HDPE	Visual
Visual Defects	None	Visual
Neck Finish	38-400	N/A

PACKAGING COMPONENTS SPECIFICATIONS

Description: **Caps 38-400 CRC, HS35/F217**

ID #: **EP-0151**

Parameter	Specification	Method
Outer Diameter (inches)	1.760 ± 0.010	Measure
Total Height (inches)	0.670 ± 0.010	Measure
Inner Cap Mouth Diameter (inches)	1.485 ± 0.010	Measure
Inner Cap Top Diameter (inches)	1.395 ± 0.010	Measure
Weight (grams)	7.0 ± 1.5	Measure
Color	White	Visual
Inner Liner	Paper backed Al foil coated Heat sealable	Visual
Shape	Round	Visual
Material	Polypropylene	Visual
Visual Defects	None	Visual
Neck Finish	38-400	Check with EP-0004,6,8 & 9

7.3.2.2 Master Packaging Batch Records

Master Packaging Batch Records describing packaging and labeling will be provided at later date when available.

7.3.2.2.1 Blinded Products

Insulin Human 7.5 mg Capsules, 190 Caps/Bottle

Placebo for Insulin Human 7.5 mg Capsules, 190 Caps/Bottle

7.3.3 **Product Labeling**

7.3.3.1.2 Bottle Label

Insulin Human 7.5 mg/ Placebo, 190 Caps/Bot

Placebo Insulin Human 7.5 mg/ Placebo, 190 Caps/Bot

Copies of the exact labels to be used in the study will be provided at a later date when available as Amendment to this IND.

7.4 Environmental Assessment

As sponsor of this IND, TrialNet-NIDDK-NIH seeks categorical exclusion from the Environmental Assessment Requirement pursuant to the provisions of *21 CFR 25-24 ©) (4)*.

Support for this request for exclusion is based on previous Agency drug application approvals for commercial formulations products of Insulin. More over, the amount of additional quantities of the above drug impacting the environment as a result of this study is minuscule.