EXHIBIT 1
Part 5 of 14

"DRAFT OF CHEMIST'S PART, LETTER TO APPLICANT"

We have completed the review of the extraction, manufacturing and controls information and request the following additional information:

Please submit any information you may have regarding the structure of erythropoeitin.

It is noted that the solution of erythropoeitin is normal serum albumin is packaged in vials and sealed. Please clarify if the vials are heat sealed or sealed with a rubber closure.

You state that the drug product retains its hormonal activity during storage in the frozen state. Please include data which demonstrates the stability of erythropoeitin.

Include a signed form 1571. (Submitted

HMR 935352

IND ASSIGNMENT AND SAFETY REVIEW TRANSMITTAL

1. IND NO.	2. DATE RECEIVED	3. NAME OF SPONSOR
41234	2-13-79	[redacted]

4. NAME OF DRUG: [redacted]

5. PHARMACOLOGIC CATEGORY/INDICATION: [redacted]

Deliver to the last addressee indicated below; cross through your name before forwarding to the next addressee.

HFD-116 — Management Technician

SAFETY REVIEW DUE DATE: [redacted]

GROUP CONSUMER SAFETY OFFICER: [redacted]

WAIVER REQUESTED: ☐ YES ☐ NO

GROUP LEADER/SUPERVISOR: [redacted]

REVIEWER: [redacted]

DATE ASSIGNED: 3/20/79

PRELIMINARY SAFETY REVIEW

I find it reasonably safe to initiate clinical studies.

☐ YES ☐ NO (If "NO," see attached memorandum)

SIGNATURE OF REVIEWER: [redacted] DATE: 3/21/79

GROUP LEADER/SUPERVISOR: [redacted]

CONCURRENCE

I concur in the above decision.

☐ YES ☐ NO (If "NO," see attached memorandum)

SIGNATURE OF GROUP LEADER/SUPERVISOR: [redacted] DATE: 3/21/79

GROUP CONSUMER SAFETY OFFICER: [redacted]

Deliver to Document Control Desk when this box is checked. ☐

HMR 935353

FORM FDA 2773 (6/75)

AM670221987

AM-ITC 01006654

IND ASSI[illegible]ENT AND SAFETY REVIEW TRANSMITTAL

1. IND NO.	2. DATE RECEIVED	3. NAME OF SPONSOR
16234	3-13-79	JM BARON, MD

4. NAME OF DRUG: Human ERYTHROPOIETIN (H-E[illegible])

5. PHARMACOLOGIC CATEGORY/INDICATION: Blood FORMATION STIMULANT STU[illegible]

Deliver to the last addressee indicated below; cross through your name before forwarding to the next addressee:

HFD-110 — Management Technician

SAFETY REVIEW DUE DATE: 3/15/79

25 DAY 4/4/79
50 DAY 4/23/79

GROUP CONSUMER SAFETY OFFICER: Pradey

WAIVER REQUESTED: ☐ YES ☐ NO

GROUP LEADER/SUPERVISOR: Temple

REVIEWER: Solo[illegible]

DATE ASSIGNED: 3/21/79

PRELIMINARY SAFETY REVIEW

I find it reasonably safe to initiate clinical studies.
☒ YES ☐ NO (If "No," see attached memorandum)

SIGNATURE OF REVIEWER: A.K. Sh[illegible] P.D.

DATE: 3/29/79

GROUP LEADER/SUPERVISOR

CONCURRENCE

I concur in the above decision.
☐ YES ☐ NO (If "No," see attached memorandum)

SIGNATURE OF GROUP LEADER/SUPERVISOR

DATE

GROUP CONSUMER SAFETY OFFICER

Deliver to Document Control Desk when this box is checked.

HMR 935354

New IND

FORM FDH 2773 (6/73)

IND 16,234

MAR 22 1979

Joseph M. Baron, M.D.
Box 420
950 East 59th Street
Chicago, Illinois 60637

Dear Dr. Baron:

We acknowledge receipt of your Notice of Claimed Investigational Exemption for a New Drug (IND) submitted pursuant to section 505(i) of the Federal Food, Drug, and Cosmetic Act. Please note the following identifying data:

IND Number Assigned: 16,234

Sponsor: Joseph M. Baron, M.D.

Name of Drug: Human Erythropoietin (H-EPO)

Date of Submission: March 2, 1979

Date of Receipt: March 13, 1979

As per your March 21, 1979 telecon with Mr. Denver Presley of this office, please sign the enclosed FD forms 1571 and 1573. Three forms should be forwarded in triplicate, identified with IND number 16,234 and addressed as follows:

Bureau of Drugs HFD-110
Attention: DOCUMENT CONTROL ROOM #16B-30
5600 Fishers Lane
Rockville, Maryland 20857

Any future communications concerning this IND should also be forwarded in triplicate, identified with the IND number assigned, and addressed as stated above.

As sponsor of the clinical study proposed in this IND you are now free to obtain supplies of the investigational drug, but it it understood that studies in humans will not be initiated prior to 30 days after the date of receipt shown above. It is further understood that you will continue to withhold or restrict such studies should we so request within that 30 day period.

HMR 935355

AM-ITC 01006656

AM670221989

You are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and Regulations. This includes the immediate reporting of any alarming reactions in either animal or human studies, and submission of progress reports at intervals not to exceed one year.

Sincerely yours,

3/21/79

Natalia A. Morgenstern
Supervisory Consumer Safety Officer
Division of Cardio-Renal
Drug Products
Bureau of Drugs

Enclosures: (4) FD Form 1571
(4) FD Form 1573
(1) DHEW Publication No. (FDA) 74-3015

cc:
Orig. IND
HFD-110
HFD-110/CSO 3/21/79
HFD-110/DPresley/cto/3/21/79

ACKNOWLEDGEMENT
IN
FORMATION REQUEST

HMR 935356

AM670221990

AM-ITC 01006657

THE UNIVERSITY OF CHICAGO
THE DIVISION OF THE BIOLOGICAL SCIENCES
AND
THE PRITZKER SCHOOL OF MEDICINE
BOX 420
950 EAST 59TH STREET
CHICAGO · ILLINOIS 60637

Department of Medicine
Section of Hematology/Oncology

Telephone
(312) 947-5013

IND 16234

March 2, 1979

Robert Temple, M.D.
Bureau of Drugs (HFD-110)
Parklawn Building
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Temple:

I am submitting the enclosed materials for a Physician-Sponsored IND for Human Erythropoietin (H-EPO). We have spoken by phone several times in the past year or so about the limited amount of available Erythropoietin for animal toxicity studies. We have completed the toxicity study in a single species (hamsters) at a daily dose level of approximately 18 times the intended human test dose over a 22 day period without evidence of adverse effect (see appended data).

I feel the submitted material supports the very high likelihood of safe administration of H-EPO to patients. In addition to learning new things about the pharmacology of Erythropoietin (using purified human hormone for the first time) we are most hopeful that it will be possible to demonstrate efficacy of this material in significantly stimulating erythropoiesis in [illegible]. Successful use of Erythropoietin in patients with renoprival anemia would be most welcome.

Thank you for your help.

RECEIVED
MAR 13 1979
DRUGS

Sincerely yours,

Joseph M. Baron

Joseph M. Baron, M.D.
Associate Professor of Medicine
Acting Chief, Section of Hematology/
Oncology

JMB/ajt
encs.

HMR 935357

AM670221991

AM-ITC 01006658

Clinical Study of Purified Human Erythropoietin (H-EPO)

Physician Sponsored IND

Investigator: Joseph M. Baron, M.D.
Associate Professor
Department of Medicine
Section of Hematology
University of Chicago
Chicago, Illinois

Physician Sponsored IND

1. Investigator: Joseph M. Baron, M.D.
Associate Professor
Department of Medicine
Section of Hematology
University of Chicago
Chicago, Illinois

2. Name of Drug: Human Erythropoietin (H-EPO)

3. Manufacturing Information:
(c) Human erythropoietin (H-EPO) has been prepared from the urine of patients with aplastic anemia. Details of the source, purification and assay of the material are in the attached reprint of Miyake, et. al. (J. Biol. Chem. 252 (15): 5558-5564, 1977). The final purification and assay of H-EPO have been performed in the laboratory of Dr. Eugene Goldwasser at the University of Chicago, Department of Biochemistry.

The hormone is diluted in Normal Serum Albumin (Human) USP (Albuspan(R), Parke Davis) at a concentration of 276 units/ml. (80,000 units/mg H-EPO protein) to maintain stability and permit appropriate volume for administration. The final dosage form was sterilized in a single batch by Nuclepore filtration in the University of Chicago Pharmacy Department, sealed in vials containing 1.9 ml. of material and frozen (total of 520 units contining approximately 6.5 micrograms of H-EPO protein per vial). The final solution was pyrogen-free and sterile (see attached certificates). The purified H-EPO was negative by Limulus assay prior to dilution in the albumin. The final product was biologically active by in vitro and in vivo assays. Long term retention of hormonal activity during storage in the frozen state has been demonstrated.

Human Erythropoietin (H-EPO)

For parenteral use only
276 units/ml

Investigator: J. Baron, M.D.
Univ. of Chicago

"Caution: New Drug-Limited by Federal/or United States Law to Investigational Use."

3. Manufacturing Information (Cont'd):

The preparation to be used in the proposed clinical test of erythropoietin is that described as fraction II in Table IV of the attached paper (Miyake, Kung and Goldwasser, J. Biol. Chem. 252, 5558 (1977).

Pyrogen (endotoxin) was removed from 1.0 ml of a fraction II concentrate containing 25,000 units of erythropoietin by centrifugation at 35,000 rpm and 2°C for 17 hours over a 0.7 ml cushion of pyrogen-free Normal Serum Albumin (Human) USP (Albuspan (R), Parke Davis). After centrifugation, 1.0 ml of the upper fraction was removed, a 0.002 ml aliquot was added to 0.1 ml of pyrogen-free saline (USP - Travenol) and tested for pyrogen by the Limulus lysate method (Sigma - E-toxate kit). We found no evidence of clotting or aggregation after 2 hours of incubation at 37°C, whereas the positive control showed an effect within 15 minutes. The remainder (0.998 ml) was dissolved in 88 ml of Normal (USP, Albuspan (R) Parke Davis) sterilized by Nuclepore filtration and vialed by the University of Chicago Hospital Pharmacy at 1.9 ml/vial. Test for sterility was done by The University of Chicago Hospital Microbiology Laboratory and it was found to be sterile. Similar handling was done for the albumin solution without added erythropoietin.

Test of the same material in rabbits, at five times the calculated human dose showed, in the three rabbits, at the end of three hours, temperature rise of 0.0°, 0.0°, and 0.04°. Another test for pyrogen by the standard USP method was done by Tox Monitor Laboratories and the results are enclosed.

Assay of the pyrogen-free erythropoietin by the marrow cell culture method (reprint enclosed) showed a concentration of 24,600 units per ml before dilution into the albumin solution. Each vial then contains 276 units of erythropoietin per ml or 524 units per vial.

4. Preclinical Information

c. Animal Toxicology

Please see attached report from Ward Richter, D.V.M. of the A.J. Carlson Animal Research Facility at the University of Chicago summarizing a toxicology study in hamsters (22 day course at 18 times the intended human daily per kilogram dose). A very limited supply of the H-EPO precludes a similar study in a second larger species.

e. There are no other animal toxicity data with H-EPO. It is effective in stimulating erythropoiesis in vitro and is not known to be cytotoxic in culture systems. H-EPO stimulates erythropoiesis in rodents in vivo. There are no human toxicology or pharmacology studies with this purified material.

5. Clinical Information

a. Rationale and Objectives

It is proposed to study the pharmacology and efficacy of H-EPO as a stimulant of erythropoiesis in man. Initial trials will be done in a small number of patients with renoprival anemia. Since the lack of erythropoietin is generally believed to be the single most significant cause of this anemic state it seems logical and especially important to test H-EPO in these patients who would appear to have the most to gain from H-EPO. Also, because these patients have lower baseline serum erythropoietin levels than those patients with comparable degrees of anemia due to other causes (e.g. iron deficiency), it is easier to raise the serum H-EPO level with infusion of smaller amounts of the hormone.

Recent rodent data (1,2) and in vitro studies (3) support the likelihood that H-EPO may be effective in stimulating erythropoiesis in human subjects with renoprival anemia.

Additional pharmacologic studies in normal volunteers and patients with anemia of chronic disease would follow if safety and efficacy are demonstrated in the initial trials. Limited amounts of H-EPO currently available preclude large scale studies.

5. b. References

1. Anagnostou, A., Barone, J., Kedo, A., and Fried, W.: Effect of Erythropoietin Therapy on the Red Cell Volume of Uremic and Non-Uremic Rats.

Brit. J. Haemat. 37: 85, 1977.