EXHIBIT 1
Part 4 of 14

8. Serum H-EPO level (by radioimmunoassay method)

9. Urinary H-EPO determinations (in patients with urine output)

Treatment:

All patients will be hospitalized. H-EPO to be administered by intermittent slow intravenous infusion of 520 units (in 1.9 ml volume over 15-20 minutes) every 12 hours. The dosage is based on pharmacokinetic considerations. Its methodology was enclosed with the submission. Plasma $T_{\frac{1}{2}}$ was considered of approximately 12 hours (according to literature). No loss by dialysis (too high molecular weight) and lack of significant urinary loss also was projected.

Treatment to last for 7 days with a subsequent observation period of 2 weeks.

The dose to be administered is to raise the average serum H-EPO concentration to 50 mu/ml (approximately 3x the average normal level of 16.5 mu/ml).

Parameters Monitored:

During and after the treatment period -

1. CBC, platelets, reticulocyte count on every other day.

2. Serum H-EPO levels daily with additional determinations after the first and last injections to evaluate disappearance time from plasma.

3. Repeat SMA-17 on days 3, 7 and 21.

4. Repeat ferrokinetics and bone marrow studies on day 10.

5. Repeat Cr^{51} red cell mass and blood volume on day 21.

6. Daily 24 hour urine collection for H-EPO assay (as available).

Evaluation:

From clinical standpoint this special investigation may proceed. The investigator is well qualified and the patients will be hospitalized

during the trial. H-EPO is a naturally occuring hormone and its use may be of value under the conditions described.

Recommendations: As stated above.

A.A. Solymossy, M.D.

cc: Orig. IND 16-234
HFD-110
HFD-110/CSO
HFD-110/ASolymossy
F/T:jp/4/3/79

R Temple 6/22/79

HMR 935343

1/1

MAY 2 4 1979

REVIEW AND EVALUATION OF PHARMACOLOGY
AND TOXICOLOGY DATA IND 16,234 (3/2/79)

Sponsor: Joseph M. Baron, M.D.

Drug: Human Erythropoietin (H-EPO) 276 units/ml

Proposed Dosage: 520 units q. 12 h. (20.8 units/kg/day)

Category: Human Hormone

Proposed Study:

Three or 4 adults with anemia of chronic renal failure who are hemodialyzed three times weekly.

Preclinical Toxicology: (U. of Chicago)

Hamsters, 4 controls, 4 treated, given "18 times intended human dose" (Not quantitatively identified but work sheets show item 25U/0.3 ml/day which is probably 183 to 250U/kg/day) for 22 days. Injection route not defined.

Results:

No evidence of adverse effect. Male gonads and spleens are heavier in treated than control hamsters.

Cited References:

A. Anagnostou, et. al., Effect of Erythropoietin Therapy on the Red Cell Volume of Uraemic and Non-uraemic Rats. Brit. J. Haemat. 37:85-91.1977.

Rats, 200 gram, 30 to 40, partially nephrectomized and a comparable number of sham-operated controls, divided into 2 groups for saline and erythropoietin S.Q. injections of 5 units(25 units/kg) 6X weekly for 13 doses.

Donor female rats received 5 u Ci (^{59}Fe) FeCl, i.v.. Blood was washed, centrifuged and resuspended to a 50% hematocrit which was utilized, i.v., 0.4 ml to calculate blood volume.

HMR 935344

Results:

I. 5 Days Post Injection

	Sham Operated			Partially Neph. Ect.		
	PCV	Blood Urea	Red Cell V.	PCV	Blood Urea	Red Cell V.
Before Injection	44	-	4.6	42	-	3.9
After Injection						
Saline	46	3.3	4.9	34	19.7	3.5
Ep.	56	3.3	7.3	54	16.0	6.7
II. 21 Days Post Injection						
Before Injection	46		5.0	38		3.7
After Injection						
Saline	47	3.3	5.0	44	12.5	4.2
Ep.	60	3.3	7.2	56	12.5	6.5

It can be seen that in this model Erythropoietin does increase the red cell mass in uraemic rats.

B. Urabe, Akio, et. al, Response of Uraemic Bone Marrow Cells to Erythropoietin In Vitro. Scand. J. Haematol 17:335-340. 1976.

Authors demonstrated that plasma from uraemic patients inhibited, in a dose dependent way, the response of normal bone marrow cells to erythropoietin.

C. Van Stone, J.C., and Paul Max, The effect of erythropoietin on the Anemia of Uremia. Abstract, American Society of Nephrology 1978.

Rats, 5/group, 4 groups, 2 surgically anephric, 2 sham operated, one of each given saline or EPO, 2 units/day/12 days. Peritoneally dialyzed daily. (About 10 units/kg).

Results:

	NTX	NTX+EPO	C	C+EPO
Bun (mg/dl)	107	100	25	16
PIT (mg/kg/day)	1.01	1.84	1.56	1.92
RBC Fe^{59} uptake (%)	48	71	74	70
Nucleated RBC/ FEMUR (X10)	0.64	2.52	2.22	2.65
HCT (%)	19	30	42	48
RBC Mass (ml/kg)	14.0	21.4	24.0	31.4

Authors conclude that EPO completely corrects the marked bone marrow depression and significantly reduces the anemia in rats.

Comments:

The hamster dose is said to be 18X the human clinical dose which could then be 374 units/kg/day, but this is not stated in the report. Item 25U/0.3 ml may be dosage, or 183 to 250 U/kg/day.

In other experiments, cited by reference, the rat dosages were 25 and 10 units/kg/day. The proposed clinical dosage is 21 units/kg/day.

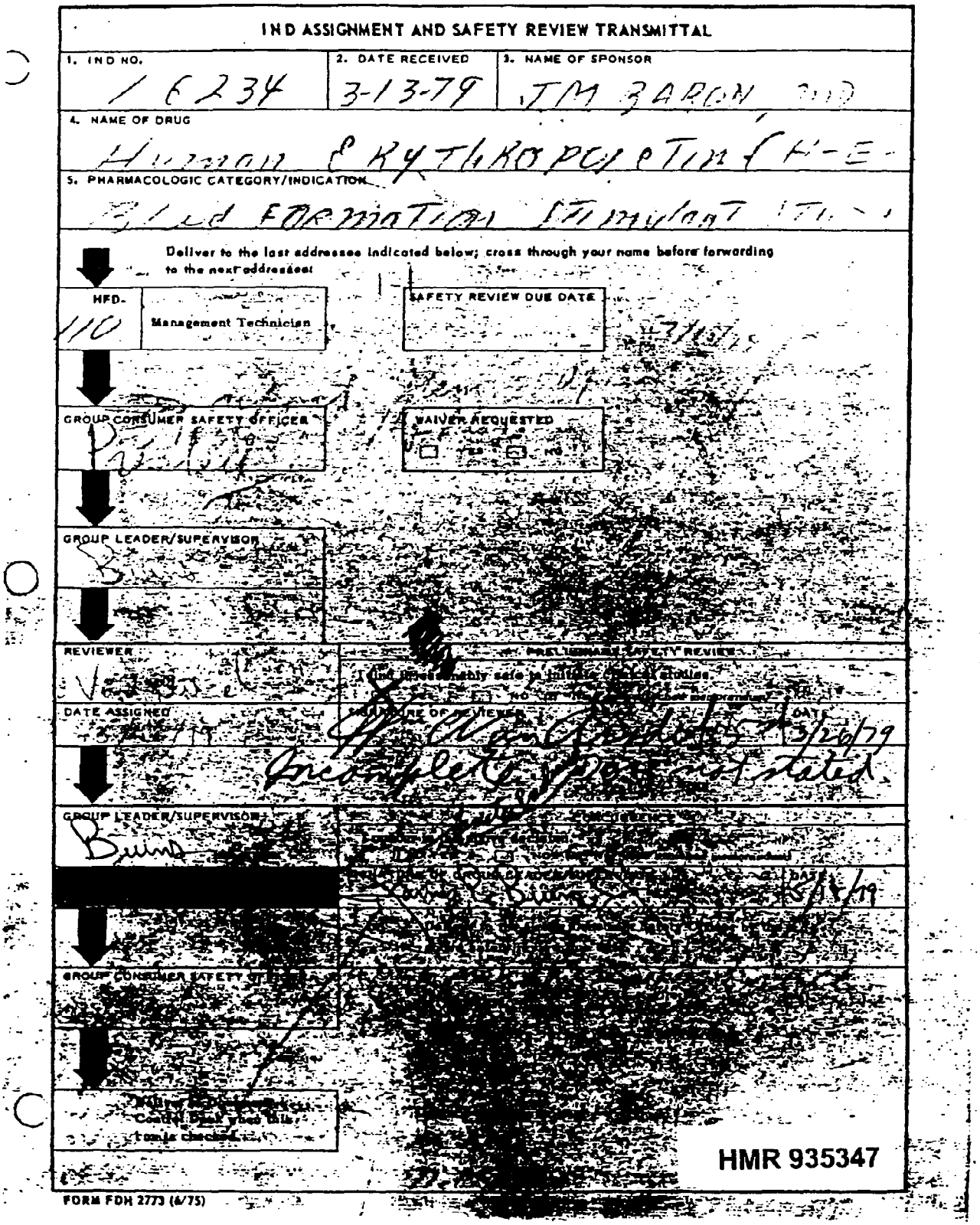
Recommendations:

It would seem that the preclinical studies support the clinical safety of this preparation, but the hamster dose should be identified, because none of the rat doses achieve the proposed clinical dosage with normal safety margin multiples.

William WanArsdel 3rd

cc: Orig. IND 16,234
HFD-110
HFD-110/CSO
HFD-110/WVanArsdel
HFD-110/R/Dinit:JBurns/5/18/79
F/T:jp/5/24/79

HMR 935346



IND ASSIGNMENT AND SAFETY REVIEW TRANSMITTAL

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

4. NAME OF DRUG: HUMAN ERYTHROPOIETIN (H-E-

5. PHARMACOLOGIC CATEGORY/INDICATION: RED CELL FORMATION STIMULANT ITS

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

GROUP CONSUMER SAFETY OFFICER

WAIVER REQUESTED YES NO

GROUP LEADER/SUPERVISOR

REVIEWER

PRELIMINARY SAFETY REVIEW

I find it reasonably safe to initiate clinical studies. YES NO

DATE ASSIGNED

SIGNATURE OF REVIEWER DATE 3/26/79

Incomplete as protocol not stated.

GROUP LEADER/SUPERVISOR

Burns

DATE 5/4/79

GROUP CONSUMER SAFETY OFFICER

Control Book Yes No
Items checked

FORM FDH 2773 (6/75)

HMR 935347

Pasley

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
CHEMIST'S REVIEW #1

MAR 30 1979

Date Completed: March 23, 1979

A. 1. IND #: 16-234

Sponsor: Joseph M. Baron, M.D.
University of Chicago
The Pritzker School of Medicine
Chicago, Illinois 60637

AF #: None

2. Product Name(s):

Proprietary: None

Non-proprietary: Human Erythropoietin

USAN: None

Compendium: None

Code name and/or number: None

3. Dosage Form(s) and Route(s) of Administration:

Injectable, 276 units per ml.

4. Pharmacological Category and/or Principal Indications:

Regulation of normal red blood cells.

5. Structural Formula and Chemical Name(s):

Human eythrcpoietin is a protein extracted from the urine of patients with aplastic anemia.

B. Initial Submission: March 2, 1979. Received Bureau of Drugs, March 13, 1979.

HMR 935348

C. Remarks. Erythropoiten is considered to be the hormonal plasma factor which stimulates red cell production. The Notice proposes to study the efficacy erythropoietin.

D. Conclusions and/or Recommendations: From a chemistry, manufacturing and controls standpoint, the study may proceed. However, there are some minor deficiencies that should be corrected. See "Draft of Chemist's Part of Letter to Applicant."

Robert J. Wolters

cc:
Orig. IND
HFD-110
HFD-110/CSO
HFD-102/Dr. Kumkumian
HFD-110/RJWolters/cto/3/27/79
R/D init. by: JLangston/3/23/79

E. Review Notes:

1. & 2. Components & Composition:

Ingredients:

Human Erythropoietin 276 units
Normal Serum Albumin (Human) qs 1 ml

Sealed in vials containing 1.9 ml (520 units) approximately 6.5 microgram per vial.

3. & 4. Facilities and Personnel:

The purification and assay have been performed in the University of Chicago, Department of Biochemistry Laboratory. Sterilization and packaging at the University of Chicago, Department of Pharmacy. Additional information is not considered necessary at this time.

5. Synthesis:

Erythropoietin is extracted from human urine of patients with aplastic anemia. The urine is pooled and deionized on a Sephadex column. Cellulose is added, filtered, dialyzed and lyophilized. The crude urine concentrate is purified by ion exchange chromatography, ethanol precipitation, gel filtration, and absorption chromatography with a 21% yield. The procedure is described in a reprint included in the Notice. Erythropoietin is an acidic glycoprotein of unknown structure with a molecular weight of 39,000. Request the Sponsor submit any information he may have regarding the structure of erythropoietin.

6. Raw Material Controls:

A reprint is included which describes the assay of erythropoietin. The method is based on the amount of labelled ferric ion uptake due to the biosynthesis of hemoglobin in calf serum produce when erythropoietin is added. This amount is compared to a control without erythropoietin.

The method has the disadvantage of detecting a form of erythropoietin which has no in vivo activity. This method is apparently the best method currently available. Acceptable.

7. Other Firms:

Tox Monitor Laboratories, Melrose Park, Illinois conducts pyrogen testing in rabbits.

8. Manufacturing and Processing:

The new drug substance is diluted with normal human serum albumin and 1.9 ml (520 units) is packaged into vials and sealed. The solution was sterilized by filtration. The product is then frozen. Acceptable.

9. Container:

The product is packaged into glass vials. It is not clear if the vial is an ampul or has a rubber closure. Request clarification.

10. Laboratory Controls:

The product is assayed and the bulk solution is tested for pyrogens by the Limulus lysate method. The packaged product is tested for pyrogens by the USP rabbit method, sterility, and assayed. Satisfactory.

11. Control Numbers:

Not considered necessary as only one batch has been made.

12. Stability:

The Sponsor states that the activity is maintained during storage in the frozen state. Request supportive data.

13. & 14. Samples and Results:

Not considered necessary at this time.

14. Labeling:

A copy of the label is included. Satisfactory.

15. & 16. Establishment Inspection and Registration:

Not considered necessary at this time.

17. From 1571, Parts 11, 12, & 13:

These parts were not included, Form 1571 was also missing. Request this information as it was not included in the original copy.

HMR 935351