



**EXHIBIT 3**

NOV 28 1995

Iron Dextran Injection, USP  
50 mg/ml, 2 ml Vials  
ANDA = 40-024  
Reviewer: James E. Chaney  
WP = 40024S.395

Luitpold Pharmaceuticals, Inc.  
Shirley, New York  
Submission Date:  
March 21, 1995

## REVIEW OF PHARMACOKINETICS AND IRON UTILIZATION STUDIES

### Biostudy Objective:

The purpose of the proposed study was to compare the relative bioavailability of the test product, DEXFERRUM™ (iron dextran injection, 50 mg/ml) produced by Luitpold Pharmaceuticals, Inc. with the reference product INFeD<sup>®</sup> (iron dextran injection, 50 mg/ml) produced by Steis Laboratories and marketed by Schein Pharmaceutical, Inc., when given to patients undergoing hemodialysis for end-stage renal disease.

Bioequivalence was determined by two methods:

- (1) Pharmacokinetics of iron dextran and
- (2) Iron utilization for hemoglobin synthesis and ferritin-related stores

The pharmacokinetics study is herein reviewed by the Division of Bioequivalence. The second part (iron utilization) was consulted to HFD-180. The Agency recently established that iron utilization study could be the pivotal study.

### General Background:

Iron dextran is indicated for the treatment of iron deficient patients in whom oral administration is unsatisfactory or impossible. Parenteral iron supplements are required in nearly all patients with dialysis associated anemia. The reference product is administered intramuscularly and intravenously.

The formulations of the test and reference products are as follows:

<u>Ingredient</u>	<u>DEXFERRUM™ (Luitpold)</u>	<u>INFeD<sup>®</sup> (Steis)</u>
Elemental Iron (as Iron Dextran)	50 mg/ml	50 mg/ml
Water for Injection, USP	q.s.	q.s.

The pH of the solution may be adjusted with sodium hydroxide and hydrochloric acid. The pH of the solution is in the range of 5.2 to 6.5 for the test and reference products and both products are isotonic. Sodium chloride is added to both products for tonicity adjustment. Iron dextran consists of a  
which is complexed to a

In June 1968, the FDA accepted Fisons Pharmaceuticals' Imferon<sup>®</sup> according to the provisions of a DESI-review. In September 1991 Luitpold filed an ANDA for its DEXFERRUM™, including a waiver request using Imferon<sup>®</sup> as the reference listed drug.

In 1991 Eisons withdrew Imferon<sup>®</sup> from distribution due to GMP problems. INFeD<sup>®</sup> (iron dextran injection, 50 mg/ml produced by Steris Laboratories) was then approved in 1992, after first being made available under a treatment IND. All subsequent applications used INFeD<sup>®</sup> as the listed reference drug. FDA refused to grant Luitpold a waiver.

#### Reasons for Denial of Waiver Requests:

Part of the basis for denial of the waiver requests was the dramatic difference in molecular weight between the test product and reference drug. Per OGD's request Luitpold compared in depth its iron dextran, 50 mg/ml with Imferon<sup>®</sup> and the current reference product, Steris' INFeD<sup>®</sup> (iron dextran, 50 mg/ml, marketed by Schein). Luitpold reported that a batch of its test product (DEXFERRUM<sup>™</sup>) had a molecular weight of \_\_\_\_\_ as determined by \_\_\_\_\_. Using the same technique Luitpold determined that the original reference product, (Imferon<sup>®</sup>) had a molecular weight of \_\_\_\_\_ and the current reference (INFeD<sup>™</sup>) had a molecular weight of \_\_\_\_\_. The iron dextran product of \_\_\_\_\_ has a reported molecular weight of \_\_\_\_\_. Thus, the molecular weight of the test product falls between the values reported for Imferon<sup>®</sup> or INFeD<sup>®</sup> and \_\_\_\_\_.

Another problem is that iron dextran is not a true solution. On 10/21/92 Luitpold requested that its product be waived based on its claim that the product is a colloidal solution. As with parenteral suspensions, parenteral colloidal solutions are considered by the Division of Bioequivalence to be a problem and waivers of *in vivo* bioequivalence studies are not granted on them. Accordingly, in the 13th edition of the Approved Drug Products with Therapeutic Equivalence Evaluations the INFeD<sup>®</sup> rating was changed from AP to BP.

#### Pharmaceutical Equivalence:

In 1993 the Suitability Petition Committee established that Luitpold's iron dextran is pharmaceutically equivalent to the reference INFeD<sup>®</sup>. Luitpold was informed that the iron dextran products would be considered as pharmaceutically equivalent without regard to the molecular weight, for regulatory purposes. In this Suitability Petition Committee meeting it was concluded that a pharmacokinetics study and an iron utilization study consisting of determining the degree of mobilization of iron from iron dextran to ferritin storage and hemoglobin synthesis should be done. Following the Suitability Petition Committee meeting the firm submitted a protocol which was found acceptable for a study to determine if DEXFERRUM<sup>™</sup> is equivalent to INFeD<sup>®</sup>, the listed product in dialysis dependent patients:

#### Background on Iron Dextran Safety:

On 7/30/92 another waiver request was submitted based mainly on literature information. This is important information but it was not totally convincing that the waiver should be granted. This information follows.

Millions of patients were treated with Imferon<sup>®</sup> (Fisons iron dextran) worldwide following the 1960's and the safety of the product has been generally recognized. Anaphylactoid reactions, characterized by sudden cardiovascular collapse and respiratory failure, have been reported to occur in 0.6 to 1.0% of patients after receiving Imferon<sup>®</sup>. These reactions respond readily to diphenhydramine, steroids and epinephrine. Once the dose is tolerated successfully, further iron dextran administration is usually not a problem if each injection does not exceed 250 mg of iron. Also, the good safety record on the iron dextran injection, 50 mg/ml produced by [redacted] as judged from [redacted] reporting of adverse reactions was emphasized by Luitpold.

The low toxicity of iron dextran as opposed to free ferric ions, is attributed to the stability of the iron dextran complex. Iron is steadily removed from the iron dextran complex by the cells of the reticuloendothelial system (RES). After the iron is separated in the RES from dextran, it is either bound to the appropriate iron binding proteins for recirculation, or it is stored for replenishment of hemoglobin iron and depleted iron reserve stores.

Data were submitted by Luitpold on the quantities of iron dextran injection, 50 mg/ml distributed by [redacted] and adverse drug reactions reported to [redacted] over 15 years. [redacted] reported one adverse effect in 20,000 ampules for its product. [redacted] iron dextran injection has a molecular weight of [redacted] which places the molecular weight of [redacted] or Luitpold's test product between the values reported for Imferon<sup>®</sup> (molecular weight of [redacted] or INFeD<sup>TM</sup> (molecular weight of [redacted] and [redacted] product. However, [redacted] product is not approved by the US FDA.

## I. PHARMACOKINETICS STUDY

### A. Criteria for Eligibility of Patients:

The patients were male or female patients 18 years or more in age undergoing high flux hemodialysis for end-stage renal disease and had life expectancies of more than 60 days. The patients were on epoetin alpha therapy for dialysis-associated anemia. The patients were iron deficient requiring parenteral iron supplementation as defined by plasma ferritin levels less than 100 mcg/L or transferrin saturation less than 20%.

The patients underwent a physical examination including vital signs (respiratory rate, temperature, pulse rate, and blood pressure), and a medical history was taken. Hematological evaluations included white blood cell count, antinuclear antibody test, rheumatoid factor, hemoglobin, hematocrit, plasma ferritin, and transferrin saturation.

Each subject signed a written consent. Prior to the start of the study the study protocol was approved by the Institutional Review Boards of [redacted]

**B. Exclusion Criteria:**

1. Active inflammatory disease, infection, or carcinoma likely to produce reticuloendothelial blockade.
2. Active gastrointestinal bleeding (hematochezia or hematemesis).
3. Elective surgery prior to study completion; nonelective surgery during the course of the study resulted in discontinuation from the study.
4. Previous sensitivity to iron dextran.
5. Oral iron supplementation within 48 hours prior to the study entry.
6. Treatment with iron dextran, except for the 0.5 ml (25 mg) test dose, within one month of the first scheduled dose.
7. Transfusion dependency or transfusion within one month of study entry.
8. Patients were required to abstain from alcoholic beverages for 48 hours prior to dosing and until the study was completed.
9. Oral glucocorticosteroid therapy

**C. Study Design:**

A single dose, open-label, randomized, two-way crossover study was conducted on 20 male or female iron-deficient patients undergoing hemodialysis for end-stage renal disease. The time between phases was one week.

Since anaphylactic and other serious reactions may occur with administration of iron dextran each patient received a 0.5 ml (25 mg) test dose of DEXFERRUM™ at nine days (-9 days) prior to the administration of its first full dose (100 mg). Two days later (-7 days) each patient was administered a 0.5 ml (25 mg) test dose of INFed<sup>®</sup>. Each subject was observed for 45 minutes after the 25 mg test dose for the development of adverse reactions.

**D. Dose:**

Two ml of the test drug, DEXFERRUM™ (iron dextran, 50 mg/ml) or 2.0 ml of the reference drug, INFed<sup>®</sup> (iron dextran, 50 mg/ml, marketed by Schein) was administered via the venous port of the dialysis tubing. Study drug administration occurred at the beginning of regular dialysis treatments. The DEXFERRUM™ lot number was 3554, and had an expiration date of 8/95. The INFed<sup>®</sup> lot number was 93F010 and had an expiration date of 12/94. The study was completed prior to the expiration of either product.

**E. Blood Sample Collection:**

Blood samples were collected at 0, 1, 2, 4, 6, 8, 24, 48, 72 and 96 hours following drug administration.

**F. Clinical Methodology:**

The clinical portion of the study was performed at

Samples were prepared according to standard operating procedures for shipment to the

During the course of the study, the site investigator, a professor of nephrology at transferred his affiliation from

Patients transferred with him, including the patient who participated as the final study subject. This study was completed with the approval of the which had reviewed the study at the time it was initiated at the site

**G. Subject Monitoring:**

Patients were managed on an outpatient basis during the treatment and follow-up periods. Adverse events and vital signs were monitored for 45 minutes following the test doses, and at each timepoint for blood collection following administration of the full iron dextran doses.

**H. Analytical Methodology:**

The analytical portion of the study was performed by

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**I. Assay Validation and Quality Control Data:**

The satisfactory performance of the total iron, transferrin-iron and iron dextran determinations over the course of 13 months is shown in Table 1. The assay pre-study validation data for all the measured compounds are summarized in Table 2 and it is satisfactory

**Table 1. Quality Control Data on Total Iron, Transferrin-Iron and Iron Dextran During the Course of the Bioequivalence Study ( $\mu\text{g/dl}$ )**

	Control I			Control II			Control III		
	Total Iron	Transferrin Iron	Iron Dextran	Total Iron	Transferrin Iron	Iron Dextran	Total Iron	Transferrin Iron	Iron Dextran
Target	178	121	57	339	99	240	674	219	455
Mean	175.9	126.7	50.3	332.8	118.0	214.8	668.1	239.7	406.9
%CV	7.5	13.7	26.9	3.0	19.4	13.0	6.1	13.2	11.1
n	51	51	51	47	47	47	45	45	45

**Table 2. Pre-study Assay Validation**

Parameter	Total Iron	Iron Dextran
Sensitivity (mcg/dl)	9	23
Linearity (mcg/dl)	Adequate to 1127	Adequate to 2000
Intra-assay Precision (%CV)	1.6-3.2	3.6-10.6
Inter-assay Precision (%CV)	2.7-6.6	4.0-16.0
Accuracy (%)	102-106	90-104
Specificity	Specific	Specific
Stability	24 hours after treatment with sodium hydrosulfite at r.t.	6 hours after filtering through alumina
Percent Recovery	102	90-103

**J. Pharmacokinetic and Statistical Analysis:**

The data in the terminal, log-linear phase were analyzed by linear regression to estimate the terminal disposition rate constant and half-life. In nearly all patients, a good estimate of the terminal disposition phase was obtained from the last four to seven data points.  $AUC_{0-\infty}$  was calculated using the trapezoidal method, and  $AUC_{0-96}$  was calculated by adding  $C_t/K_e$  to  $AUC_{0-t}$ . Four different AUC's were determined for each subject and for each product.

The first AUC was that determined from zero to 96 hours ( $AUC_{0-96}$ ). This area included the time zero concentration even if that value was not zero.

- The second area,  $AUC_{0-96 \text{ adjusted}}$ , was derived from  $AUC_{0-96}$ . The  $AUC_{0-96}$  was adjusted for the apparent iron dextran which was present at time zero to give  $AUC_{0-96 \text{ adjusted}}$  as follows:

$$AUC_{0-96 \text{ adjusted}} = AUC_{0-96} - C_0/K_z$$

where  $K_z$  is the terminal disposition rate constant.

- The third type of AUC presented was  $AUC_{0-inf}$ .  $AUC_{0-inf}$  was calculated as

$$AUC_{0-inf} = AUC_{0-96} - C_{96}/K_z$$

- The fourth type of AUC presented was the  $AUC_{0-inf \text{ adjusted}}$  determined as follows:

$$AUC_{0-inf \text{ adjusted}} = AUC_{0-96 \text{ adjusted}} - C_{96}/K_z$$

ANOVA's were performed using SAS GLM procedures. The arithmetic mean and %CV were calculated for each pharmacokinetic parameter. The geometric means and maximum likelihood estimates (least squares estimates, or point estimates) of the ratio of DEXFERRUM™ to INFED<sup>R</sup> for  $AUC_{0-inf}$  and  $C_{max}$  were calculated by the firm for  $AUC_{0-inf}$  and  $C_{max}$ . The ANOVA included sequence, subject within sequence, phase, and drug treatment in the statistical model. The 90% confidence levels were determined for  $C_{max}$  and  $AUC_{0-inf}$ .

#### K. Results:

Twenty patients, 10 males and 10 females, started the study. Ten patients were enrolled at each treatment site. All 20 subjects finished the study.

The maximum likelihood estimates (least squares point estimates) for  $AUC_{0-96}$ ,  $AUC_{0-inf}$ , and  $C_{max}$  derived from serum concentrations which were not adjusted for time zero concentrations are 1.29, 1.64 and 1.04, respectively (Table 3). The corresponding

**Table 3. Geometric Means of Iron Dextran Pharmacokinetic Parameters, Least Squares Point Estimates and 90% Confidence Intervals Following Intravenous Dosing of Dextran<sup>R</sup> (Test) and INFED (Reference), N=20**

Parameter (Units)	Geometric Means		Least Squares Point Estimates	90% Confidence Intervals
	Test	Reference		
(Not Adjusted For Iron Dextran Concentrations at Time Zero)				
$AUC_{0-96}$ (hr- $\mu$ g/dl)*	159642	124023	1.29	
$AUC_{0-inf}$ (hr- $\mu$ g/dl)	237417	144702	1.64	
$C_{max}$ ( $\mu$ g/dl)	3292	3162	1.04	
(Adjusted For Iron Dextran Concentrations at Time Zero)				
$AUC_{0-96}$ (hr- $\mu$ g/dl)*	155208	116143	1.34	
$AUC_{0-inf}$ (hr- $\mu$ g/dl)	230875	135756	1.70	
$C_{max}$ ( $\mu$ g/dl)	3207	2973	1.08	

\* Derived from reviewer's SAS analysis

90% confidence intervals are

The confidence

intervals do not fall within the limits of 80% to 125% for  $AUC_{0-4}$  or for  $AUC_{0-inf}$ . The point estimates obtained from the analysis of log transformed data for  $AUC_{0-4}$  and  $AUC_{0-inf}$  did not fall within 0.80 to 1.25. However, treatment did not have a statistically significant effect on  $C_{max}$ . Similar point estimates and confidence intervals were obtained if the parameters were derived from serum concentrations which were adjusted for time zero concentrations. Also, there was no significant sequence effect between patients who received the test product first and patients who received the reference product first.

The iron dextran arithmetic mean pharmacokinetic parameters  $AUC_{0-4}$ ,  $AUC_{0-inf}$ ,  $C_{max}$ ,  $T_{max}$ ,  $T_{1/2}$ ,  $\log_{10}AUC_{0-4}$ ,  $\log_{10}AUC_{0-inf}$ , and  $\log_{10}C_{max}$  parameters are shown in Table 4. Also, the test-to-reference ratios for  $AUC_{0-4}$ ,  $AUC_{0-inf}$  and  $C_{max}$  are shown in Table 4. The area under the iron dextran concentration curve was significantly greater, half-life was longer, and clearance rate slower after DEXFERRUM<sup>®</sup> than after INFED<sup>®</sup>. The pharmacokinetic parameters  $AUC_{0-4}$ ,  $AUC_{0-inf}$  and  $C_{max}$  derived from serum concentrations which are not adjusted for time zero concentrations and which are adjusted for time zero concentrations are very similar.

**Table 4. Arithmetic Mean Iron Dextran Pharmacokinetic Parameters (%CV) and Mean Test/Mean Reference Ratios Following Intravenous Dosing with 100 mg of Iron Dextran (DEXFERRUM<sup>®</sup> and INFED<sup>®</sup>). N=20**

Parameter (units)	Means		Test/Reference <sup>a</sup>
	Test	Reference	
(Not Adjusted For Iron Dextran Concentrations at Time Zero)			
$AUC_{0-4}$ (hr- $\mu$ g/dl) <sup>b</sup>	186004 (43)	128303 (27)	1.51
$AUC_{0-inf}$ (hr- $\mu$ g/dl)	290113 (49.6)	149421 (26.5)	2.02
$C_{max}$ ( $\mu$ g/dl)	3480 (34.4)	3280 (26.7)	1.06
$T_{max}$ (hr)	3.41 (53.9)	2.75 (53.6)	1.24
$T_{1/2}$ (hr)	58.9 (32)	34.2 (19)	1.72
$\log_{10}AUC_{0-4}$ <sup>b</sup>	5.20	5.09 (2.27)	
$\log_{10}AUC_{0-inf}$	5.376	5.160 (2.18)	
$\log_{10}C_{max}$	3.52	3.50 (3.54)	
(Adjusted for Iron Dextran Concentration at Zero Time)			
$AUC_{0-4}$ (hr- $\mu$ g/dl) <sup>b</sup>	180971 (43)	119695 (26)	1.51
$AUC_{0-inf}$ (hr- $\mu$ g/dl)	282138 (49.9)	139302 (24.1)	2.02
$C_{max}$ ( $\mu$ g/dl)	3396 (34.9)	3080 (26.4)	1.10
$T_{max}$ (hr)	3.41 (53.9)	2.75 (53.6)	1.24
$T_{1/2}$ (hr)	58.9 (32)	34.2 (19)	1.72
$\log_{10}AUC_{0-4}$ <sup>b</sup>	5.19	5.07	
$\log_{10}AUC_{0-inf}$	5.363	5.133	
$\log_{10}C_{max}$	3.51	3.47	

<sup>a</sup>Reviewer calculated <sup>b</sup>Derived from reviewer's SAS analysis

The test-to-reference ratios for individual patients for the pharmacokinetic parameters  $AUC_{0-12}$ ,  $AUC_{0-inf}$  and  $C_{max}$  are shown in Table 6. Only one subject (subject 309) had an  $AUC_{0-inf}$  T/R ratio that fell between 0.80 and 1.20. These test-to-reference ratio data for individual patients are summarized in Table 5. The median ratios from unadjusted time zero concentrations for  $AUC_{0-12}$ ,  $AUC_{0-inf}$  and  $C_{max}$  were 1.48, 1.90 and 1.05, respectively. The mean ratios from unadjusted time zero concentrations for  $AUC_{0-12}$ ,  $AUC_{0-inf}$  and  $C_{max}$  were 1.42, 1.87 and 1.06, respectively. The ranges of ratios from unadjusted time zero concentrations for  $AUC_{0-12}$ ,  $AUC_{0-inf}$  and  $C_{max}$  were 0.12 to 2.05, 0.13 to 2.77 and 0.5 to 1.44, respectively. Of the 20 subjects the number of subjects with T/R ratios that fell within the limits of 0.80 to 1.20 for  $AUC_{0-12}$ ,  $AUC_{0-inf}$  and  $C_{max}$  using unadjusted time zero concentrations were 3, 1 and 16, respectively. The test-to-reference ratios for individual patients for the pharmacokinetic parameters  $AUC_{0-12}$ ,  $AUC_{0-inf}$  and  $C_{max}$  derived from serum concentrations which were not adjusted for time zero concentrations and which were adjusted for time zero concentrations are very similar.

Table 5. Iron Dextran Test/Reference Ratios for $AUC_{0-12}$ , $AUC_{0-inf}$ and $C_{max}$ Following Intravenous Dosing of DEXFERRUM <sup>®</sup> and INFed <sup>®</sup> (N=20)						
	Not Adjusted for Time Zero Concentration			Adjusted for Time Zero Concentration		
	$AUC_{0-12}$	$AUC_{0-inf}$	$C_{max}$	$AUC_{0-12}$	$AUC_{0-inf}$	$C_{max}$
Minimum						
Maximum						
Median	1.48	1.90	1.05	1.56	1.90	1.1
Mean	1.42	1.87	1.06	1.49	1.95	1.10
No. of subj in T/R range of 0.8-1.2	3	1	16	3	1	15

L. **Summary of adverse experiences:**

Adverse reactions were determined by: volunteered comments by patients, elicited information during observation by nephrology nurses, monitoring vital statistics during the administration and observation phases, and evaluation of laboratory results.

The total number of exposures to the test and reference iron dextran in this study is too small to precisely estimate adverse reaction rates, but the adverse reactions noted were mild for both drugs and no severe or immediate reactions could be related to their administration.

Hypotension is a customary reaction in dialysis procedures. Though the study

design made it impossible to discern between dialysis-related and drug-related hypotension, the firm statistically analyzed the occurrence of hypotension during the test and study doses and found no relationship between changes in blood pressure and treatment type.

The characteristic concurrent clinical complications of the study group combined with the normal adverse experiences encountered during hemodialysis, especially vaso-instability resulting from fluid shifts during high flux dialysis, made it impossible to discern between dialysis-related and drug-related hypotension.

**M. Comments on Pharmacokinetics Submission:**

1. The data set is confounded with residual carryover effect. Several subjects had non-zero pre-dose concentrations, even in the first period (because of the test doses of the test and reference drugs on days -9 and -7, respectively). Given the long half-life of the drug, a 6-7 day washout is inadequate.
2. In this study  $AUC_{0-inf}$  is not a reliable measurement, since the extrapolated portion is too large.
3. Analytical data collected by Luitpold on nine lots of the reference product INFeD<sup>®</sup> document significant variation in molecular weights of the reference product.
4. The confidence intervals do not fall within the limits of 80% to 125% for  $AUC_{0-4}$  or for  $AUC_{0-inf}$ .
5. Treatment did not have a statistically significant effect on  $C_{max}$ .
6. The point estimates obtained from the analysis of log transformed data for  $AUC_{0-4}$  and  $AUC_{0-inf}$  did not fall within 0.80 to 1.25.
7. The mean serum DEXFERRUM<sup>™</sup> concentrations for each time point for Luitpold's DEXFERRUM<sup>™</sup> and Steris Laboratories' INFeD<sup>®</sup> were not submitted nor were the mean serum profiles (graphs) presented.

## II. IRON UTILIZATION STUDY

In the iron utilization study bioequivalence was established by determining the iron utilization for hemoglobin synthesis and ferritin-related stores. Iron utilization was estimated by determining iron stores and new hemoglobin synthesis prior to dosing and 30 days after the last of five 100 mg doses. This study was conducted between October 1993 and August 1994 at \_\_\_\_\_ The analytical portion of the study was performed by \_\_\_\_\_

- A. **Pertinent Paraphrased Remarks of HFD-180 Director's Cover Letter on Medical Officer's Review of Iron Utilization Study:**
  1. In the iron utilization study Luitpold's DEXFERRUM<sup>™</sup> (iron dextran injection, 50 mg/ml) is at least as good as INFeD<sup>®</sup> (iron dextran injection, 50 mg/ml) produced

by Steris Laboratories and marketed by Schein Pharmaceutical, Inc.

2. If the firm plans to administer the product intramuscularly a phase IV bioavailability study might be requested and a postmarketing surveillance should be useful to pick up failures of therapeutic effect by that route if they occur.
- B. Summary and Conclusions Iron Utilization Study from Medical Reviewer:**
1. DEXFERRUM<sup>®</sup> and INFeD<sup>®</sup> treatment did not result in statistically different mean values of percent mobilization.
  2. Both total iron and ferritin demonstrated a statistically significant time effect but no treatment effect. DEXFERRUM<sup>®</sup> showed a larger decrease in the TIBC (total iron binding capacity) and a larger increase in the % transferrin saturation. Hemoglobin did not demonstrate either a statistically significant effect on time or treatment. For serum iron there was marginally significant interaction between time and treatment. There was an increase in serum iron for the DEXFERRUM<sup>®</sup> treated patients, but virtually no increase for the INFeD<sup>®</sup> treated patients.
  3. There was no overall difference in the proportion of patients experiencing no adverse events, a hypotensive reaction after two hours, a probable dialysis-related adverse event, or a possible drug reaction.
  4. When all data relative to hypotensive events were analyzed there was no evidence to suggest that DEXFERRUM<sup>®</sup> compared to INFeD<sup>®</sup> administration was complicated by a higher rate of hypotensive reactions.
  5. The other adverse reactions noted during the study can also have a stronger relationship to the dialysis treatment than to the drugs administered.
- C. Recommendations of Medical Reviewer on the Iron Utilization Study:**
1. In the iron utilization study DEXFERRUM<sup>®</sup> has performed as well or better than the listed drug, INFeD<sup>®</sup>, in providing the patients with a supplement of iron for replenishment of iron stores and new hemoglobin synthesis.
  2. Safety of iron dextran complexes had been established prior to this study.
  3. DEXFERRUM<sup>®</sup> is approvable.

### III. OVERALL COMMENTS OF DIVISION OF BIOEQUIVALENCE

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1. Luitpold claims in its application that its product is intended only for intravenous administration. The reference product is administered intramuscularly and intravenously. However, Luitpold's labelling states that its DEXFERRUM<sup>®</sup> is to be administered intramuscularly and intravenously. Both bioequivalence studies (pharmacokinetics and iron utilization) were done using only the intravenous route of administration. Therefore, the firm should submit a post approval commitment to perform a Phase IV study using the intramuscular route of administration.

2. This approval would constitute the first generic approval for iron dextran. Therefore, since it is a new generic product it will require a biostudy inspection.

#### IV. OVERALL RECOMMENDATIONS ON APPLICATION

1. The pharmacokinetics arm of the bioequivalence study conducted by Luitpold Pharmaceuticals, Inc. on its iron dextran injection, 50 mg/ml, comparing it to INFeD<sup>®</sup> (iron dextran, 50 mg/ml, produced by Steris Laboratories and marketed by Schein Pharmaceutical, Inc.) after intravenous administration shows that the test product is bioavailable.
2. The iron utilization arm of the bioequivalence study conducted by Luitpold Pharmaceuticals, Inc. on its iron dextran injection 50 mg/ml, comparing it to INFeD<sup>®</sup> after intravenous administration has been found to be acceptable by the Division of Bioequivalence per recommendations of the medical reviewer (section C of the iron utilization part of this review).
3. From the bioequivalence point of view, the application is approvable as a 505b(2) application provided the firm agrees to submit a post approval commitment to perform a Phase IV study using the intramuscular route of administration per comment 1 of Part III. The final approval of the application will depend on the results of a routine FDA biostudy inspection per comment 2 of Part III.

The firm should be advised of the recommendations.

*James E. Chaney*  
James E. Chaney, Ph.D.  
Division of Bioequivalence  
Review Branch I

Date 11/16/75

RD INITIALED YCHuang  
FT INITIALED YCHuang

*James E. Chaney* Date 11/16/75

Concur:

*Keith K. Chan*  
Keith K. Chan, Ph.D.  
Director, Division of Bioequivalence

Date: 11/28/75

cc: ANDA 40-024 (original), HFD-600 (Hare), HFD-630, HFD-344 (Viswanathan),  
HFD-652 (Huang, Chaney), Drug File, Division File

JEC/111595/WP#40024S.395