CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 018439

Trade Name: MVC-PLUS

Generic Name: AQUEOUS MULTI-VITMIN FOR INTRAVENOUS INFUSION

Sponsor: ASCOT HOSPITAL PHARMACEUTICALS

Approval Date: 07/13/82

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: 018439

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 018439

APPROVAL LETTER

NDA 18-439

JUL 13 1982

Ascot Hospital Pharmaceuticals
Attention: Arnold M. Schacter
8055 N. Ridgeway Avenue
Skokie, Illinois 60076

Dear Mr. Schacter:

Please refer to your new drug application submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act, and in response to the July 13, 1979 Federal Register notice on conditions for marketing parenteral multivitamin products, for the preparation MVC Plus, a two-vial product for intravenous infusion.

We also refer to your submission dated June 18, 1982, which contains revised final printed labeling for this product.

We have completed our review of this new drug application as submitted with final printed labeling, and it is "conditionally approved." Please note that this conditional approval applies only to the two-vial product (vial A and vial B), manufactured by Ascot Injectables, which is the subject of NDA 18-439. This conditional approval does not apply to any container system other than that referred to above.

In addition, reference is made to your communication of June 24, 1982, in the compatibility studies performed on MVC Plus. This amendment contains minimal information regarding

Final approval of this application will depend upon the following:

1) Submission of a detailed description, including a

APPEARS THIS WAY
ON ORIGINAL

2) Satisfactory results for the

3) Satisfactory completion of clinical studies with MVC Plus, as required in the above mentioned Federal Register notice.

Sincerely yours,

/S/ /S/

APPEARS THIS WAY
ON ORIGINAL

Solomon Sobel, M.D.
Director
Division of Metabolism and
Endocrine Drug Products, HFD-130
Office of New Drug Evaluation
National Center for Drugs and Biologics

cc:
NDA Orig.
HFD-130
HFD-130/KEllsworth/7/7/82;rch/7/8,12/82(6254B)

CONDITIONAL APPROVAL

R/D Init. by REAstep/7/7;SSobel/7/9;HBNunn for DJKertesz/7/9;OAlford/7/9;
Guerlguian/7/9/82

/S/ 7/12/82

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 018439

MEDICAL REVIEW(S)

NDA 18-439
MVC Plus
Parenteral Multivitamins
Wang 5074B

Ascot Hospital Pharmaceuticals, Inc.
Submission dated 4-6-82
Received by MO 4-13-82
Reviewed 4-15-82

Medical Officer's Review and Evaluation of NDA Report

This submission contains new data on those vitamins which we agreed at our meeting with the firm January 22, 1982 were not within acceptable limits. The vitamins have all been satisfactorily assayed after addition to large volume parenterals except pantothenic acid. They say that it is possible to for the clinical study, and they will be able to determine from assay of that acid if blood levels are maintained. Therefore they request that we approve the product without compatibility studies showing the availability of pantothenic acid. This is acceptable. If levels are adequately maintained in fairly long term studies, we will know that amounts administered were adequate. The only problem would be if the metabolite was formed from the inactivated vitamin so that pantoic acid was normal in spite of unusable vitamin being administered. This seems unlikely since pantothenic acid is not a problem with the vitamin preparations of other manufacturers.

In the submission of 12-8-81, Table 2 showing MVC Plus compatibility, and in this submission, table 3 showing the same compatibility, worst possible case are based on storage The package insert Dosage and Administration section says, "After MVC Plus is diluted in an intravenous infusion, the resulting solution should be refrigerated unless it is to be administered immediately, and in any event should be administered within 48 hours." The submission of 8-28-81 contains the original compatibility data. The 48 hr data was after . Vitamin A was and was Other values were all right, and all were acceptable at 24 hours at Folic acid was in solution C. The data should have been analysed at 24 hours and apparently would show satisfactory stability at that time.

The vial labels submitted are not legible. I am particularly concerned that the instructions "For use together with Vial A" or "with Vial B" are not going to prevent use of one vial only, which happened with USV's MVI.

This preparation is now approvable with changes in the label to say, "administer within 24 hours," and legible wording for vials and cartons that both vials are to be used for one dose.

Draft of Letter to Sponsor: The data on compatibility are acceptable, but do not justify saying in the first sentence of the last paragraph that after addition to intravenous infusion, they should be administered "within 48 hours." This should say "within 24 hours."

The vial label is not legible. With other products, there has been confusion about the contents of the vials, resulting in administration of one vial in the belief that a complete dose was being given. The vial must state clearly and legibly that both vials are to be used for one dose.

/S/
Gloria Troendle

cc:OrigNDA, HFD-130,
HFD-130/GTroendle, HFD-180

APR 27 1982

NDA 18-439
MVC Plus
Parenteral Multivitamins

Ascot Hospital Pharmaceuticals
Submission dated 12-8-81
Received by MO 12-9-81
Reviewed 12-11-81

Medical Officer's Review and Evaluation of NDA Report

This submission responds to our deficiency letter of 11-30-81. Labeling changes are being made. The draft package insert is satisfactory except as noted below in regard to recommendations for storage after addition to LVP's.

The response to our request that packages say that both vials are to be used for a single dose is to put "For use together with Vial B" and "For use together with Vial A" on the respective vials. The box in which both vials are packaged should also contain a statement such as "Both vials are to be used for a single dose."

The protocol is revised to include the changes requested and is satisfactory.

The response to our concerns about the potency of the vitamins after storage and then addition to LVP's and about the the marked variation in assay results is to resubmit the data with results at I had used the lowest value obtained at any time period up to 24 hr with dark refrigeration. Actually it appears that if the stability losses are really manufacturing losses and were already assumed in the vitamins added to the LVP's, only have lows on addition to LVP's that put them of label claim. When added to Travasol and 50% dextrose in Travenol plastic bags, was initially, at 6 hr and at 12 hr. It was above in the other solutions. Vitamin C was initially, at 6 hr, at 12 hr and at 24 hr when added to 5% dextrose in refrigerated in dark. It was above of label claim when added to the other solutions.

Many of the determinations of vitamins are well above the amounts added to the solutions, indicating a great inaccuracy of the assays used. This is disturbing, but I do not know what accuracy we should expect. The sponsor seems to be saying that greater accuracy is impossible, but other manufacturers do not seem to have had this much trouble. For the most part they seem to come out on the high side so maybe they are not detecting values below 90% of label in other cases where accurate measurement would show it. Vitamin D is included in this submission although it was not in the previous one. After addition of of vitamin D label claim, assays detect which is than theoretically possible. B_1 is added and detected, an of B_2 is added and detected. an of B_6 is added and detected, an of B_{12} is added and detected, an of biotin is added and detected, an . Pantothenic acid still has not been assayed for compatibility with LVP's. The chemist must tell us whether the assay results are satisfactory for the other vitamins.

Draft of letter: The Dosage and Administration section of the package insert should say, "After MVC Plus is diluted in an intravenous infusion, the resulting solution should be refrigerated unless it is to be administered immediately, and in any event should be administered within 6 hours."

DEC 11 1981

Please submit the results of the studies on compatibility of with large volume parenterals as soon as possible. The application cannot be approved without these results.

/S/

Gloria Troendle

cc:Orig NDA
HFD-130
HFD-130/GTroendle
HFD-180

I recommend a Non-approval action at this stage, based on a wider critique of the submission, to wit:-

The vitamin assay data are, generally speaking quiet unreliable (Chemist may like to confirm this); therefore, the medical implications of that fact (unreliability of Vitamin assay data) are totally unacceptable. We cannot permit clinical studies with a preparation whose titer is not properly ascertained.

/S/ 12/15/81

APPEARS THIS WAY
ON ORIGINAL

NDA 18-439
M.V.C. Plus
Parenteral Multivitamins

Ascot Hospital Pharmaceuticals, Inc.
Submission dated 8-28-81
Reviewed 10-19-81

Medical Officer's Review and Evaluation of NDA Reports

This submission responds to our letters of May 12 and July 8, 1981. It contains a revised protocol for the clinical studies, corrected labels, and the results of the compatibility and stability studies. I delayed writing up my review because I wanted to discuss the methods and results with the chemist, but since we should respond within 60 days on these vitamins, I will not wait any longer.

I. Protocol for the clinical studies that will be conducted on the vitamins after approval.

12 subjects at least 18 years of age and requiring TPN are to be studied. Four are to have a right colectomy due to Ca of the colon, 4 Crohn's disease which is to be treated with in-patient TPN and 4 with Crohn's disease to be treated with out-patient TPN. Vitamins will be determined in whole blood, plasma or serum at baseline, after 1 day and after 5, 10 and 15 weeks of therapy and at unspecified intervals up to 24 weeks if patients remain on TPN for that long. Blood samples are to be drawn after termination of a bottle of TPN and for those out-patients who receive their TPN at night they will be drawn in the morning.

The time of drawing blood samples is in response to our request to know that vitamins are not to be drawn while they are being infused. It seems to me that they should be drawn as long a time after infusion as possible within a 24 hr period. That would mean that if vitamins are added to only one bottle a day or if infusions are given during one 8 hr period (night for out-patients) blood samples should be drawn before the start of the next infusion containing vitamins.

I do not know why the protocol is so restrictive about the number of patients of a given category that will be studied, but the total number of subjects is very small and perhaps this is an attempt to obtain patients with a fair chance of being on TPN for 4 months. 12 will probably be an adequate number if they are on treatment for 4 months and if serum values are within normal range in almost all of them at almost all of the sampling times. Since a number of companies are doing studies with the same formulation I would be inclined to accept this number of patients. It is possible that the differences in stability and compatibility result in delivery of slightly different amounts of the vitamins from the different preparations, but I think that our separate studies of these parameters combined with a small clinical trial should give us adequate information.

The age range should not be restricted to patients over 18 since the vitamin preparation is for anyone 11 years or more of age.

II. Labeling.

The submitted labels at least agree with the package insert as to the contents of the two vials. The problem which was recognized for MVI of consumers using one of the two vials and thinking they had added a complete vitamin

OCT 1981

formulation could occur with this product. USV is being asked to put on the carton that both vials are to be used for one dose. Other changes suggested in the letter which is now circulating and which relate to making their labeling compatible with the new format for labeling should also be made in the labeling for this product. This includes statements on carcinogenesis, pregnancy, nursing mothers, pediatric use and overdosage.

III.Stability and Compatibility.

The results of the dexpanthenol microbiological assay were not satisfactory due to carmelization of the dextrose solutions, and the vitamin D assays were not completed so the compatibility assays are incomplete.

I thought that we discussed with them the unacceptability of addition of extra vitamin to the solutions so that the amounts contained would be easier to assay, but there are still amounts of vitamin in excess of the stated overages added in the 0 time assay for vitamins A, C, B_1, B_2, B_6, folic acid, B_{12} and biotin in at least one of the three solutions. These amounts all exceed added vitamin amounts by more than 10% and could be within the limits of variability of the methods only if variation of more than 10% is expected. This is one of the things I hoped to discuss with Mr. Alford.

I also do not know whether the overages have been changed since the stability studies were done, because the values found initially in the stability study were often lower than the values found after 3 months. The following chart uses the lowest value (in percent of label claim) whether it was initial or 3 months (S-low). It also shows the amount added with overages (Add-over). The third column is the low observed in any of the three solutions within 24 hours after adding the vitamins to large volume parenteral solutions (C-low) The fourth column is the calculated % of Add-over (C-low/Add-over) and the fifth is this % times S-low to get the amount that would be left if the amount added were the lowest amount left after storage instead of the new solution with the overages intact. All values are in percent of label claim.

Vitamin	Add-over	S-low	C-low	% of Add-over	Remaining
A				60	
D					
E				80	
C				27	
B_1				93	
B_2				100	
B_6				80	
Niacinamide				88	
Pantothenic acid					
Folic acid				66	
B_{12}				70	
Biotin				82	

Only 3 vitamins remain at 90% or better of label claim and one of these was added to 150% initially. Vitamins A and B_{12} are below the acceptable limits even though they are initially 150 and 200% of label claim if the overages are

indeed what is stated. If less was present at the outset then the S-low values should be higher and a few more of the vitamins might meet the acceptable range.

Recommendation and Draft of Letter:

1. With regard to the protocol for clinical studies submitted as Exhibit 1 we make the following suggestions:

   a. It would be preferable to draw blood samples within the 24 hour period as long as possible after the infusion of the last dose. This would mean that if the in-patients had all of the day's dose of vitamins added to one bottle each day the sample would be drawn just before beginning the infusion of that bottle which contains the day's supply of vitamins. For the out-patients the sample would be drawn as late in the day as practicable.

   b. Also, the protocol should not limit subjects to those more than 18 years of age since subjects as young as 11 might receive this formulation.

2. With regard to the labeling that was submitted as Exhibit 2 we make the following recommendations to make the labeling conform to the new labeling format:

   a. Under PRECAUTIONS, add a subsection CARCINOGENESIS, with a statement that studies on carcinogenesis have not been performed.

   b. Also, under PRECAUTIONS, add subsections PREGNANCY and NURSING MOTHERS. These sections should contain statements that vitamin requirements for pregnant and lactating women may exceed those of non-pregnant and non-lactating women, and that the Recommended Dietary Allowance for those conditions should be met.

   c. Also, under PRECAUTIONS, add a subsection PEDIATRIC USE. The AMA formulation is recommended for children 11 years or older. It is not appropriate for younger children and infants mostly because it has less Vitamin D than the pediatric recommendation. It would be satisfactory to say that safety and effectiveness in children below the age of 11 have not been established.

   d. Before the DOSAGE and ADMINISTRATION section, add a section OVERDOSE, which should contain a statement concerning the possibility of hypervitaminosis A or D.

   e. The label and carton should have a statement that both vials are to be used for a single dose."

3. With regard to the Stability and Compatibility studies we request clarification of the following:

   a. Were the overages that are stated in Exhibit 5 of the submission present in the vitamins used for the stability studies in Exhibit 7?

If they were, initial losses of many of the vitamins are very high. If they were not, what amounts of the vitamins were present?

b. Were these overages and no more present in the vitamins added to the TPN solutions for the compatibility studies in Exhibit 4? If so, how is it possible to have so much more of the vitamins found at the various time intervals up to 24 hours later?

c. For the formulation to be acceptable, it is necessary that total losses in shelf life and on addition to TPN solutions and storage for at least 6 hours not result in vitamin levels that are less than 90% of label claim. Only vitamins B_1, B_2 and niacinamide appear to meet this criteria.

/S/

Gloria Troendle

cc:Orig NDA
HFD-130
HFD-130/GTroendle
HFD-180

APPEARS THIS WAY
ON ORIGINAL

/S/ 10/31/91

/S/ 10/22/91

APPEARS THIS WAY
ON ORIGINAL

NDA 18-439
MVC-Plus
Parenteral Multivitamins

Ascot Hospital Pharmaceuticals
Submission dated 5-19-81
Reviewed 5-22-81

Medical Officer's Review of NDA Protocol

This letter says that the company wants verbal permission to start the compatibility study. The protocol calls for studying the compatibility of MVC-Plus after mixing with Travesol 5.5% amino acids/electrolytes + HSO_3 in plastic and Aminosyn 7% amino acids/electrolytes + HSO_3 in glass. Each will be mixed with 50% dextrose/saline before addition of the MVC-Plus. Solutions will be sampled immediately and after 6 and 12 hrs storage at 5°C. At 16 hr a portion of the remaining solution is removed from the refrigerator and stored at room temperature for 8 hr and sampled then. The remaining solution is removed from the refrigerator at 40 hr and stored at room temperature for 8 hr and the final sample taken at that time. All storage at room temperature is in light and all storage at 5°C is in dark. The bisulfite (HSO_3) will be assayed from the solution at the beginning of the study. This protocol appears to be satisfactory to me.

Recommendation: Review by the chemist, and if satisfactory, Dr. Simon should be called and told that the protocol is acceptable.

/S/

Gloria Troendle

cc:Orig NDA
HFD-130
HFD-130/GTroendle
HFD-180

MAY 25 1981

NDA 18-439
MVC Plus
Adult Multivitamins Parenteral

Ascot Hospital Pharmaceuticals, INC.
Submission dated 3-27-81
Reviewed 4-9-81

Medical Officer's Review and Evaluation of NDA Resubmission

The letter with this submission says that our questions are answered and MVC Plus should now be conditionally approved in accordance with the Federal Register Notice. This submission raises considerably more questions than it answers. We cannot be sure just what is going into the Ascot multivitamins since this disagrees with the previous submission and with what representatives of the company told us at a recent meeting.

Tab number 5 is for labeling. The package insert does not agree with the vial label about the contents of the vial, in that the package insert says that butylated hydroxyanisole is 0.005% and the vial label says it is 0.0005%, and the package insert says polysorbate 20 is 0.028% while the vial label says it is 0.28%. Neither of these agrees with the previous statement of composition, submission of 1-7-80, tab 8, pg 00202, which does not include any polysorbate 80 and says that polysorbate 20(tween 20) is 1.6%, that butylated hydroxytoluene is 0.006% and BHA is 0.0015%. This labeling agrees between vial and package insert that polysorbate 80 is 1.6% and BHT is 0.002%. Also the package insert lists all 12 vitamins for vial A and 3 of the same vitamins also in vial B. This would give 200% of the 3 vitamins, biotin, B_{12}, and Folic acid. At a recent meeting the company representatives said that their product is an exact copy of one of the approved preparations. The preparation most nearly resembling this one is MVI and amounts of these ingredients are different as well as amounts of the actual vitamins added. This company has made only minimal overage additions of vitamins, while USV has larger overages for most vitamins and above the 125% stated in the Federal Register for some. All of this is disturbing as the inconsistencies leave us unsure just what the company is doing. But we know they are marketing this product without approval. The labeling is generally a copy of the MVI labeling and is acceptable except for the statement of contents.

Previous submissions said there would be a Pediatric Formulation. This says they will not market any pediatric preparation.

A stability study protocol was submitted previously, but no stability study results.

At the recent meeting they requested to be allowed to use the compatibility studies done by the other company (presumably USV) whose product they claimed to have an exact copy of. They said they are too small to be expected to do such studies. They were told that this was not possible and they would have to have at least some of them completed before the product would be approvable.

Results are submitted of a preliminary compatibility study using 5.5% Travasol Injection with Electrolytes mixed with 50% Dextrose Injection, to which 5cc of vial A and 5cc of vial B. Samples taken at 0, 6, 12, and 24 hours storage at room temperature were analysed for the 12 vitamins. It appears that a 50% excess of ascorbic acid and riboflavin and a 35% excess of thiamine were added "for assay purposes only". Conditions of light during storage are not mentioned. The results reported are that D and Dexpanthenol were too low for valid assay. All others are above 100% of claimed value at 6 and 12 hr except B_{12}. It was 78% at 0, 73% at 6, 92% at 12 and 56% at 24 hrs. Ascorbic acid to which 50% excess was added was 145% at 24 hr, riboflavin was 141%, and thiamine was 132%. At 24 hr A was 84% and E 92%. These results are not acceptable.

We asked for a more detailed protocol and got the information that 18 patients are to be used who are on TPN for at least 2 of the diseases suggested by the AMA report. They are to be studied 5 or 16 weeks, and samples are to be collected weekly. It is confusing that the "Period of measurement" section only mentions 5 weeks. I specifically asked previously for information on the time of drawing blood samples relative to the dosing. This request was apparently not understood.

Comments: The most disturbing thing about this submission is the feeling that the company does not know what they are doing. I believe they are trying to copy a formulation that is approved, but I do not trust them to do it well. We must have clarification on the first points. I presume that the Chemist will comment on the discrepancies, the lack of stability studies, and the rest of the submission, which is primarily controls information. We should request further compatibility studies with different assays so that they can assay all of the vitamins. I imagine they will run into difficulty assaying the vitamins in blood samples also. I presume the Chemist will also comment on this.

/S/

Gloria Troendle

cc:Orig NDA
HFD-130
HFD-130/GTroendle
HFD-180

I recommend that we have a meeting with the scientific staff of the Company.

/S/

4/13/81

NDA 18-439
Multi Vitamin Concentrate for Infusion, Adult
Parenteral multivitamins Children

Ascot Hospital Pharmaceuticals, Inc.
Submission dated 9-23-80
Received by MO 12-18-80
Reviewed 12-22-80

Medical Officer's Review and Evaluation of NDA Amendment MOR #2

This is a letter responding to our letter of 3-26-80. Most of the responses are to the chemistry requests. Three responses are to medical comments.

1. Labeling is submitted. The separate vial contents for Vial A, adult, vial B, adult, vial A, Pediatric, and vial B, pediatric are listed and then the rest of the insert seems to be a common one for adult and childrens use. The copies should be separated and the adult insert should say that it does not contain vitamin K and it may be necessary to give this separately. Warnings should include that pyridoxine can decrease the efficacy of levodopa in the treatment of parkinsonism, and some information on the toxicity of vitamin A and vitamin D should appear under adverse reactions.

2. They were asked to perform compatibility studies but they say that to request this is onerous and unreasonable. They say that we must ask LVP manufacturers to do this. They should be told that such tests were required of LVP manufacturers before approval of their solutions in plastic, but any new manufacturer of LVP or SVP is expected to do the studies.

3. They say that they will test the formulation in children as requested. They submitted general plans for studies. Before approval it will be necessary to have more detailed protocols approved.

Draft of Letter to Sponsor: 1. The labeling as submitted is not satisfactory. Separate drafts for adult and pediatric preparations should be submitted. These drafts should include a warning that pyridoxine can decrease the efficacy of levodopa in the treatment of parkinsonism, and information on the toxicity of vitamins A and D. The adult insert should say that vitamin K is not included in the formulation and supplements of vitamin K may be needed.

The ingredients listed for the pediatric formulation for vial A give an incorrect amount of dexpanthenol. The AMA recommendation was 5 mg, not 50 mg.

The word refrigerator is misspelled on the last page of the draft insert.

2. The compatibility studies as requested in our letter of 26 March 1980 must be completed before the application can be approved. Studies done by large volume parenteral manufacturers were required prior to their marketing of their products in plastic containers. They are not required to test every new product that comes onto the market for addition to their solutions.

3. A more detailed protocol for clinical studies should be submitted by the time the compatibility studies are completed. This protocol should include such details as the administration of the drug and time of drawing blood for the vitamin determinations, and an estimate of the number of subjects that will be studied short term and long term.

/S/ 1/14/81 /S/ DEC 31 1980

cc: Orig. NDA
HFD-180 HFD-130
HFD-130/G.Troendle/12-30-80

Gloria Troendle

NDA 18-439
Multivitamin Concentrate
Adult and Pediatric Parenteral Multivitamins

Ascot Hospital Pharmaceuticals, Inc
Submission dated 1-7-80
Reviewed 2-7-80

Medical Officer's Review and Evaluation of Original NDA

1. General Information

   a. Name of drug: Multivitamin Concentrate
   b. Adult and pediatric parenteral multivitamins for intravenous use.
   c. Proposed indication: In Emergency Feedings: Surgery, extensive burns, fractures and other trauma, severe infectious diseases, comatose states, etc. may provoke a 'stress' situation with profound alterations in the body's metabolic demands and consequent tissue depletion of nutrients. As a result, wound healing may be impaired, enzyme activity disturbed, hematopoietic tissues affected; hypoproteinemia and edema may appear; convalescence is thus prolonged.
   d. The total dose will be contained in 2 vials containing 5 ml each and intended for infusion after dilution into a large volume parenteral (e.g. D5W).

2. Manufacturing Controls: See Chemistry Review. A protocol is submitted for stability studies including assay methods. Stability will be tested at 5°C and at room temperature.

3. Pharmacology: See Pharmacology Review.

4. Clinical Background. This submission is in response to the Federal Register notice of 13 July, 1979. The vitamin preparations currently marketed by this firm will have to be removed from the market because they are similar to vitamins found to be 'not effective' by the DESI review panel. Removal need not be until after approval of effective vitamin formulations as long as this submission is active in securing approval for a formulation that meets the AMA guidelines.

5. Clinical Studies. An outline is submitted for clinical studies to insure that the proposed formulation supplies the requirements of each of the vitamins without causing excessive tissue concentrations of any single vitamin. Subjects are to be for the adult formulation and neonates to 17 for the pediatric formulation, and to suffer from maladsorption, bowel obstruction, hypermetabolic states, renal failure, hepatic failure or cancer. Efficacy is to be maintenance of blood and urine concentrations within normal limits in at least 90% of patients in a majority of disease states. They propose serum or whole blood analyses on all of the vitamins, but offer the alternate of doing urine for niacin and pantothenic acid. Measurements for the long-term studies are to be every 3 weeks.

   The submission says, "Once guidelines are issued and finalized for this testing, every effort will be made to perform these studies in collaboration with other manufacturers, as recommended in the Federal Register." (p. 142) Also in speaking of investigators, it says, "This will be provided at such time that final guidelines for acceptable clinical studies are published in the Federal Register." (p.237)

FEB 11 1980

6. Labeling Review. No labeling is submitted.

7. Conclusions.

The indication does not mention total parenteral nutrition, which may be given for the conditions described, but may also be used in newborns for prematurity, or other conditions not mentioned. TPN should be mentioned.

No mention is made of doing compatibility studies with TPN solutions. This should be done with storage up to 48 hours unless vitamin losses are such that further storage is not warranted. It should be done under conditions of light and dark unless light storage does not result in excessive losses. It should be done in solutions of 5% dextrose in normal saline and in two amino acid solutions with 50% dextrose.

Since the pediatric formulation is designed to be used in children to the age of 11 years, the ages suggested for testing this formulation are not appropriate and the pediatric formulation should be tested in neonates to 11 years.

No guidelines are to be published for the clinical studies to be done on these formulations and the sponsor must be so informed.

8. Recommendation: The above conclusions should be sent to the sponsor.

/S/

Gloria Troendle

Note: In the list of ingredients on pg. 164 section 6 vitamin E is not included, but since it is included in the list on pg167 section 7 it appears that it will be in the formulation.

/S/

cc: Orig. NDA
HFD-180
HFD-130
HFD-130/GTroendle/rch/2/8/80

/S/

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 018439

CHEMISTRY REVIEW(S)

Division of METABOLIC AND ENDOCRINE
Drug Products (HFD-130)
Chemist's Review # 7/

Date Completed: June 29, 1982

A.1. NDA/~~IND~~# 18-439

Applicant/Sponsor

Ascot Hospital Pharmaceuticals
8055 N. Ridgeway Avenue
Skokie, Illinois 60076

2. Product Names: MVCI

Proprietary:

Non-proprietary:

3. Dosage Form and Route of Administration: Solution for IV infusion

4. Pharmacological Category and/or Principal Indication: Vitamin

5. Structural Formula and Chemical Name:

B.1. Initial Submission:

2. Amendments: June 18, 1982 and June 24, 1982

3. Supporting INDs and DMFs:

C. Remarks:

A review of the package insert included in the subject submission is being done by medical officer.

D. Conclusions:

Manufacturing and controls are adequate pending receipt of information regarding assays for Vitamin D and Pantothenic acid. It is concluded that the application can now be conditionally approved as per section 505(b)(3)(4)and(5) of the Act.

E. Recommendations: Conditional approval of NDA with medical disciplines concurrence.

JUL 7 1982 Reviewing Chemist: /S/ 7/1/82

Date Completed: April 28, 1982

A.1. NDA/~~IND~~ # 18-439

Applicant/Sponsor

Ascot Hospital Pharmaceuticals
8055 N. Ridgeway Avenue
Skokie, Illinois 60076

2. Product Names: MVCI

Proprietary:

Non-proprietary:

3. Dosage Form and Route of Administration: Solution for IV infusion

4. Pharmacological Category and/or Principal Indication: Vitamin

5. Structural Formula and Chemical Name:

B.1. Initial Submission:

2. Amendments: April 6, 1982

3. Supporting INDs and DMFs:

C. Remarks:

See MOR dated April 15, 1982

D. Conclusions:

MAY 25 1982

Manufacturing and controls information is deficient. However, it is concluded that the application is approvable on a conditional basis.

E. Recommendations:

DJKertesz/5/11/82

Reviewing Chemist: Oscar Alford/4/28/81

/S/ 5/11/82

Division of METABOLIC AND ENDOCRINE
Drug Products (HFD-130)
Chemist's Review #5

Date Completed: October 22, 1981

A.1. NDA/~~XXX~~ # 18-439

Applicant/Sponsor: Ascot Hospital Pharmaceuticals
Skokie, Illinois 60076

2. Product Names: MVCI

Proprietary:

Non-proprietary:

3. Dosage Form and Route of Administration: Solution for IV infusion

4. Pharmacological Category and/or Principal Indication: Vitamin

5. Structural Formula and Chemical Name:

B.1. Initial Submission:

2. Amendments: August 20, 1981

3. Supporting INDs and DMFs:

C. Remarks: See our R/WF letters dated May 12, 1981 and July 8, 1981

D. Conclusions:

Manufacturing and controls are unsatisfactory. See deficiencies with regard to "Formulation" in October 19, 1981 MOR with which I concur.

E. Recommendations: Rev/W.F. letter should be sent to applicant listing deficiencies and also communicated by phone.

See addendum to Dr. Troendle's part in letter.

Reviewing Chemist: /S/

Division of METABOLIC AND ENDOCRINE
Drug Products (HFD-130)
Chemist's Review #4

Date Completed: June 4, 1981

A.1. NDA/~~XXX~~ # 18,439

Applicant/Sponsor: Ascot Hospital Pharmaceuticals
Skokie, Illinois 60076

2. Product Names: Multivitamin concentrate for infusion (MVCI)

Proprietary:

Non-proprietary:

3. Dosage Form and Route of Administration: Solution for IV infusion

4. Pharmacological Category and/or Principal Indication:
Vitamin

5. Structural Formula and Chemical Name:

B.1. Initial Submission:

2. Amendments: May 21, 1981

3. Supporting INDs and DMFs:

C. Remarks: See 5-22-81 medical review of subject submission.

D. Conclusions:

Manufacturing and controls remain unsatisfactory as stated in chemist review #3.

E. Recommendations:

/S/ 6/24/81

Reviewing Chemist: O. E. Alford/6/5/81

cc:
D-130
HFD-130/OEAlford/6/5/81/sw/6/22/81
R/D init. by: DJKeresz/6/16/81
Wang NO.

Division of METABOLIC AND ENDOCRINE
Drug Products (HFD-130)
Chemist's Review #3

Date Completed: April 8, 1981

A.1. NDA/~~XXXX~~ # 18-439

Applicant/Sponsor: Ascot Hospital Pharmaceuticals
Skokie, Illinois 60076

2. Product Names: Multivitamin concentrate for Infusion (MVCI)

Proprietary:

Non-proprietary:

3. Dosage Form and Route of Administration: Solution for IV infusion

4. Pharmacological Category and/or Principal Indication: Vitamin

5. Structural Formula and Chemical Name:

B.1. Initial Submission:

2. Amendments: March 27, 1981

3. Supporting INDs and DMFs:

C. Remarks: See our letter of March 2, 1981 requesting correction of specific manufacturing and control deficiencies. Only the adult formulation will be marketed, thus evaluation of the pediatric formulation is no longer necessary.

D. Conclusions:

Manufacturing and controls are unsatisfactory in that several deficiencies still require correction

E. Recommendations:

/S/ 5/13/81

Reviewing Chemist: O. E. Alford

HFD-130/OEAlford/4/8/81/sw/4/27/81
R/D init. by: DJKertesz/4, /81

Division of Metabolic and
Endocrine
Drug Products (HFD-130)
Chemist's Review #2

A.

1. NDA 18-439
   Applicant/Sponsor: Ascot Hospital Pharmaceuticals
   Skokie, Illinois 60076

2. Product Names: Multivitamin Concentrate for Infusion (MVCI)

3. Dosage Form and Route of Administration: Solution for IV infusion

4. Pharmacological Category and/or Principal Indication: Vitamin

B.

1. Amendments: 9/23/80

2. Supporting INDs and DMFs:

C. Remarks: A currently marketed product requiring minimal manufacturing and controls data. See our letter of 3/26/80 itemizing manufacturing and controls deficiencies.

D. Manufacturing and controls are unsatisfactory. A R/WF letter to issue.

E. Recommendations:

/S/

Reviewing Chemist:

2/20/81

cc: Orig., NDA
HFD-130/OAlford/tjs/2/4/81(8124A)
R/D init. by DJKertesz/2/2/81

APPEARS THIS WAY
ON ORIGINAL

Division Name: MEDP/HFD-130
Chemist's Review #1
Reviewing Chemist: O.E. Alford
NDA #18-439 Date Completed: February 28, 1980

A. 1. NDA #18-439

Applicant/Sponsor: Ascot Hospital Pharmaceuticals, Inc.
Attention: Mr. Irving C. Udell, President

2. Product Names: Multivitamin Concentrate for Infusion (MVCI)

3. Dosage Form and Route of Administration:
Solution for IV infusion

4. Pharmacological Category and/or Principal Indication:
Vitamin

B. 1. Initial Submission: January 7, 1980

2. Supporting INDs and DMFs:

C. Remarks: The FR notice of July 13, 1979 requires that an NDA be submitted for this presently marketed product. Minimal manufacturing and controls data are required.

D. Conclusions: Manufacturing and controls are unsatisfactory. A R/WF letter to issue.

E. Recommendations:

/S/ 3/10/80
O.E. Alford

cc: Orig. NDA
HFD-102/Kumkumian
HFD-130
HFD-130/OEAlford/2/28/80;rch/3/6/80(1583A)

R.D. init. by D.J.Kertesz 3/5/80

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 018439

PHARMACOLOGY REVIEW(S)

NDA 18-439
Multivitamin product MVC

January 21, 1980
Ascot Hospital
Pharmaceuticals

Review and Evaluation of Pharmacology and Toxicology Data

The NDA is submitted in compliance with the Federal Register notice of July 13, 1979 and October 19, 1979 for the marketed product MVC containing a combination of water soluble and fat soluble vitamins.

No issues for Pharmacology at the present time.

/S/

Victor Berliner, Ph.D.

cc: Orig. NDA
HFD-180
HFD-130
HFD-130/Pharmacology
HFD-130/VBerliner,1/21/80,rch,1/31/80

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 018439

ADMINISTRATIVE DOCUMENTS

RECORD OF TELEPHONE CONVERSATON/MEETING

DATE: June 4, 1981

NDA NUMBER: 18-439

IND NUMBER:

TELECON/MEETING

INITIATED BY: ☐ APPLICANT/SPONSOR ☒ FDA

MADE: ☐ BY TELEPHONE ☐ IN PERSON

PRODUCT NAME: MVCI

FIRM NAME: Ascot Hospital Pharmaceuticals

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD: Dr. Lionel N. Simon (Vice President)

TELEPHONE NO.

On June 1 and 3 I was called by Dr. Simon inquiring as to our conclusions regarding their protocol for "Compatibility" studies which is dated 5-19-81. I told him that I would call and advise him upon completion of my review. Thus the following call was made:

Dr. Simon was given the comments stated in chemist review #4. I also told him that his firm had the option of exercising the protocol as submitted as far as intervals for determining compatibility or adopt our recommendations stated in comment #4 of the chemist review.

I expressed my concern regarding the "freezing and thawing" of samples being used in the study. I pointed out the possibility of deterioration of the vitamins through the subject procedures. Additionally I questioned the amount of overages to compensate for this possible "partial vitamin destruction". I was told that this would be explained in their submission responding to our 5-12-81 R/WF letter.

APPEARS THIS WAY ON ORIGINAL

SIGNATURE: /S/ 6/24/81

Oscar E. Alford /6/5/81

DIVISION:

FORM FD 2587 (7/77)

ORIGINAL IND/NDA

NDA 18-439 May 5, 1981

Multivitamin Concentrate for Infusion
Ascot Hospital Pharmaceuticals, Inc.

Minutes of Meeting with Sponsor:

PRESENT:

Representing Ascot:	Mr. Irving Udell, President of Ascot Dr. Lional Simon, Consultant in Regulatory Affairs Mr. Harold Siegel, Regulatory Affiars Dr. Muriel Loran, Physiologist, Vitamin Metabolism Mr. Lelan Matson, Vice-President, Scientific Associates, Chemical Analyst
Representing FDA:	Dr. Solomon Sobel Dr. Gueriguian Dr. Troendle Dr. Kertesz Ms. Carter

Purpose of Meeting: FDA requested this meeting with the sponsor to discuss the deficiencies of the resubmission of March 27, 1981.

Dr. Troendle discussed the deficiencies listed in her medical review and Dr. Kertesz presented the chemistry deficiencies.

Concerning the discrepancies in the amounts of vitamins between the vial label and the package insert, the firm responded that they have made these corrections.

With regard to the sensitivity of the assays, the chemist representing the firm explained that analysis was difficult for some of the vitamins and additional amounts of the vitamins were added for assay purposes. Dr. Troendle emphasized that stability and compatability study results must be submitted.

The firm also pointed out that they do not have the technology for assaying vitamin D and Dexpanthenol. They were given a reference, Dr. Hector DeLuca, for methodology of vitamin D detection and Dr. Gueriguian said he would obtain a reference for Dexpanthenol detection.

Dr. Loran discussed the clinical aspects and the problems of interpreting the data when patients vary from disease states such as liver, kidney, and pancreateic diseases to post surgery. It was suggested that the firm submit protocols for clinical studies which, according to the Federal Register Notice of July 13, 1979, can be carried out after the drug has been conditionally approved.

The firm agreed to clarify their corporate structure. In the original application, the manufacture of the drug was to be performed by [redacted] However, in the March 27, 1981 resubmission, Environmental Impact Analysis Reports were provided for both [redacted] with the explanation that Ascot Injectables is a subsidiary of [redacted] who is an alternate manufacturer of the product.

The firm inquired whether or not conditional approval of the drug would be delayed until validation in FDA laboratories. They were told that there is constant contact with the FDA laboratories and if all other conditions are being satisfied, then there probably would not be a delay.

The firm representatives also explained that they are considering a different type of packaging which would eliminate some of the manipulation now required with vial A and vial B.

Conclusions: The firm intends to revise and submit plans for clinical studies and would like to meet with FDA staff prior to embarking on these studies.

A letter will be sent to the company listing all of the deficiencies which have been discussed during this meeting.

Linda Carter
Consumer Safety Officer/HFD-130

cc:NDA
HFD-130
FDA Participants
HFD-130/LCarter
FT/em/5/20/81/0009A

APPEARS THIS WAY ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 018439

CORRESPONDENCE

NDA 18-439

JUN 7 1982

Ascot Hospital Pharmaceuticals, Inc.
Attention: Mr. Irving Udell
8050 N. Lawndale Avenue
Skokie, Illinois 60076

Gentlemen:

Please refer to your new drug application dated January 7, 1980 submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act and in response to the July 13, 1979 Federal Register notice on conditions for marketing parenteral multivitamin products, for the preparation Multivitamin Concentrate for Infusion.

We also refer to your resubmission of April 6, 1982.

We have completed our review of this application as submitted with printed labeling; however, before it may receive conditional approval, the labeling must be revised as follows:

a) The vial label is not legible. With other products, there has been confusion about the contents of the vials, resulting in administration of one vial only in the belief that a complete dose was being given. The vial must state clearly and legibly that both vials are to be used for one dose. In addition, the name and address of your firm must be displayed in a conspicuous manner on the label.

b) The data on compatibility are acceptable, but require a revision of the labeling under the "Dosage and Administration" section. The end of the first sentence of the last paragraph should be changed from "within 48 hours" to "within 24 hours".

Sincerely yours,

/S/ 6/4/82

Solomon Sobel, M.D.
Director
Division of Metabolism and
Endocrine Drug Products, HFD-130
Food and Drug Administration

cc: NDA Orig.
HFD-130
HFD-130/KEllsworth/5/27/82;rch/5/28,6/1 /82(5665B)
R/D init. by REastep/5/27/:OEAlford/6/1;DJKertesz/6/2;GTroendle/6/2/82
REV/WAITING FIRM

/S/ 6/4/82

NDA 18-439

JAN 27 1982

Ascot Hospital Pharmaceuticals, Inc.
Attention: Irving C. Udell
8050 N. Lawndale Avenue
Skokie, Illinois 60076

Gentlemen:

Please refer to your new drug application dated January 7, 1980, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for the preparation Multivitamin Concentrate for Infusion.

We acknowledge receipt of your communication dated January 12, 1982 requesting withdrawal of your new drug application for the preparation Multivitamin Concentrate for Infusion.

In compliance with your request and in accord with section 314.7 of the regulations under the Federal Food, Drug, and Cosmetic Act, the application with respect to this preparation is regarded as withdrawn. This withdrawal does not prejudice any future filing of the application. Further, this withdrawal will not effect the status of your submission with regard to the requirements of the Federal Register Notice of July 13, 1979. You may request that the information in the application you have withdrawn be considered in connection with any resubmission.

Sincerely yours,

/S/ 1/21/82

Solomon Sobel, M.D.
Director
Division of Metabolism and
Endocrine Drug Products, HFD-130
Food and Drug Administration

cc:
NDA Orig. /S/ 1/26/82
HFD-616
HFD-130 /S/ 1/26/82
HFD-130/REAstep/1/20/82
HFD-130/EJones/1/20/82;rch/1/26/82(3812B)

WITHDRAWAL

NOV 30 1981

NDA 18-439

Ascot Hospital Pharmaceuticals, Inc.
Attention: Mr. Irving Udell
8050 North Lawndale Avenue
Skokie, Illinois 60076

Dear Mr. Udell:

Please refer to your new drug application dated January 7, 1980, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act and in response to the July 13, 1979 Federal Register notice on conditions for marketing parenteral multivitamin products, for the preparation Multivitamin Concentrate for Infusion.

We also refer to your August 20, 1981 amendment in response to our letters of May 12 and July 8, 1981. We have completed our review of the application as amended, but before conditional approval may be granted, the following protocol and labeling deficiencies must be corrected and a revised protocol as well as revised labeling must be submitted for our review:

1. With regard to the protocol for clinical studies submitted as Exhibit I we have the following recommendations:

   a. It would be preferable to draw blood samples within the 24 hour period as long as possible after the infusion of the last dose. This would mean that if the in-patients had all of the day's dose of vitamins added to one bottle each day the sample would be drawn just before beginning the infusion of that bottle which contains the day's supply of vitamins. For the out-patients the sample would be drawn as late in the day as practicable.

   b. Also, the protocol should not limit subjects to those over 18 years of age since subjects as young as 11 might receive this formulation.

2. In order that the labeling be in accord with the "Content and Format of Labeling for Human Prescription Drugs" which was published in the Federal Register on June 26, 1979 and May 16, 1980 we recommend the following:

   a. Under the DESCRIPTION section of the package insert, in the paragraph beginning "'Aqueous' multivitamin formula," insert "with polysorbate 80" after the word "medium".

   b. Under PRECAUTIONS, add a subsection CARCINOGENESIS, with a statement that studies on carcinogenesis have not been performed.

c. Also, under PRECAUTIONS, add subsections PREGNANCY and NURSING MOTHERS. These sections should contain statements that vitamin requirements for pregnant and lactating women may exceed those of non-pregnant and non-lactating women, and that the Recommended Dietary Allowance for those conditions should be met.

d. Also, under PRECAUTIONS, add a subsection PEDIATRIC USE. The AMA formulation is recommended for children 11 years or older. It is not appropriate for younger children and infants. It would be satisfactory to say that safety and effectiveness in children below the age of 11 have not been established.

e. Before the DOSAGE and ADMINISTRATION section, add a section OVERDOSE, which should contain a statement concerning the possibility of hypervitaminosis A or D.

f. The label and carton should have a statement that both vials are to be used for a single dose.

3. Concerning the stability and compatibility studies we request clarification of the following:

a. Were

If they were, initial losses of many of the vitamins are very high. If they were not, what amounts of the vitamins were present?

b. Were these overages (and no more) present in the vitamins added to the TPN solutions for the compatibility studies in Exhibit 4? If so, how is it possible to have so much more of the vitamins found at the various time intervals up to 24 hours later?

c. For the formulation to be acceptable, it is necessary that total losses in shelf life and on addition to TPN solutions and storage for at least 6 hours not result in vitamin levels that are less than 90% of label claim. Only vitamins B_1, B_2 and niacinamide appear to meet this criterion.

4. For the compatibility studies (Exhibit 4) please explain why some of the vitamin levels in samples kept in the light at 23°C are higher than in corresponding samples kept in the dark at 5°C.

Your cooperation will be appreciated.

Sincerely yours,

/S/ 11/27/81

Solomon Sobel, M.D.
Director
Division of Metabolism and
Endocrine Drug Products, HFD-130
Food and Drug Administration

cc:
NDA Orig. ✓
HFD-130
HFD-130/LCarter/11/13,24/81;rch/11/10,18,24,81(2720B)

R/D init. by REAstep/11/10/81;OAlford/11/13,20/81;GTroendle/11/18,24/81;
DJKertesz/11/18,24/81;JGuerigulan/11/24/81

/S/ /S/ 11/25/81

NDA 16-43[illegible]

JUL 8 1981

Ascot Hospital Pharmaceuticals, Inc.
Attention: Mr. Irving Udell
8050 North Lawndale Avenue
Skokie, Illinois 60076

Dear Mr. Udell:

Please refer to your new drug application dated January 7, 1980 submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act and in response to the July 13, 1979 Federal Register notice on conditions for marketing parenteral multivitamin products, for the preparation Multivitamin Concentrate for Infusion.

We also refer to your communication of May 19, 1981. Your proposed protocol for determining compatibility has been evaluated and we have the following comments and requests:

1. The protocol is erroneously entitled "Bioavailability Study" instead of "Compatibility Study".

2. Solution "C" in the proposed protocol should be composed of 50% Dextrose/water and the respective ratio should be specified.

3. We recommend that all manufacturers of parenteral multivitamin preparations perform compatibility studies using three different containers, namely glass, polyvinyl chloride and polyolefin. The supplier(s) as well as specifications of each of the three container materials must be provided.

4. At the end of the compatibility experiments, analyses must be performed on samples of the infusion mixture for the determination of

It is understood from the discussion by telephone on June 4, 1981 between your representative Dr. Lionel N. Simon and Mr. Oscar E. Alford of this Administration that you may in the future choose to alternatively perform compatibility determinations according to our recommendation to other manufacturers of multivitamin preparations. The subject recommendation states that compatibility be determined at the following intervals: (1) initial; (2) 8 hours; and (3) 24 hours under the following storage conditions: (1) room temperature exposed to light; (2) room temperature in darkness; (3) refrigeration in darkness; and (4) refrigeration exposed to light.

Additionally it is understood that a response from you regarding the requests of our May 12, 1981 letter will be forthcoming and will include a description of the "Freezing" and "Thawing" procedures referenced in your "Compatibility" protocol as well as overage amounts where applicable that will appear in the formulation.

Your cooperation will be appreciated.

Sincerely yours,

/S/ 7-8-81

Solomon Sobel, M.D.
Director
Division of Metabolism and
Endocrine Drug Products, HFD-130
Food and Drug Administration

cc:
NDA Orig.
HFD-130
HFD-130/LCarter;rch/6/29,7/2/81(0711B)

/S/ 7/2/81 /S/ 1/6/81

/S/ 9/8/81

R/D init. by REastep/6/24/81; OAlford/6/29/81,
DJKertesz/6/30/81

/S/ 7/8/81

R/WF

/S/ 7-8-81

MAY 12 1981

NDA 18-439

Ascot Hospital Pharmaceuticals, Inc.
Attention: Mr. Irving Udell
8050 North Lawndale Avenue
Skokie, Illinois 60076

Dear Mr. Udell:

Please refer to your new drug application dated January 7, 1980, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act and in response to the July 13, 1979 Federal Register notice on conditions for marketing parenteral multivitamin products, for the preparation Multivitamin Concentrate for Infusion.

We also refer to your resubmissions of September 23, 1980 and March 27, 1981, and to the May 5, 1981 conference between your firm and FDA staff. As a follow-up to the conference, we are listing our requests which were discussed at that meeting.

From the medical standpoint we have the following comments and requests:

1. With regard to the proposed protocol for clinical studies, it is not necessary that all of the vitamins be assayed weekly. Assay at 5 weeks, 10 weeks, 15 weeks and at terminiation of TPN would suffice. On the other hand, 16 weeks is not quite 4 months and it would be preferable to continue the study if TPN is to continue.

2. Also regarding the proposed clinical protocol, the request for information on the time of drawing blood was made in order to determine the relationship of sampling to administration of the vitamins; samples should not be taken during the infusion of MVC Plus.

3. Between the vial label, the package insert, and the submission of 1-7-80, there are a number of discrepancies in the statements of the contents of the preparation. These discrepancies should be clarified. Those substances for which there are discrepancies are:

Substance	vial label	pkg insert	subm.of 1-7-80
polysorbate 80			
polysorbate 20			
butylated hydroxyanisole			
butylated hydroxytoluene			

4. The vitamins listed on the package insert include vitamin B_{12}, folic acid and biotin in both vial A and vial B, but vial labels do not. If they are included in both vials the total amount of these vitamins in the recommended 5cc from each vial is double what is recommended by the AMA.

5. The compatibility studies must be done with assays sufficiently sensitive to detect the vitamins after dilution in large volume parenteral solutions. It is not satisfactory to add additional vitamin for purposes of assay or to report that the vitamins are too low for valid assay.

6. Perhaps, if an assay is not sufficiently sensitive to detect a vitamin after dilution in large volume parenteral solutions, it will not be sufficiently sensitive for valid assay in body fluids. This should be considered in selecting assays for the clinical protocol.

7. The completed compatibility study indicates that vitamin B_{12} falls below 90% of label claim after very brief storage at room temperature. It may be that refrigeration will result in adequate preservation of vitamin B_{12} levels.

8. It is necessary to ensure that adequate vitamin is present after storage for the length of time for which the expiration date provides, and after subsequent addition to large volume parenteral solutions. Both stability studies and compatibility studies must be completed before this determination can be made. It may be necessary to increase the amount of overage on some of the vitamins if present amounts do not provide sufficient vitamin for the losses during storage both before and after addition to large volume parenteral solutions.

9. Compatibility studies in 2 amino acid solutions mixed with 50% dextrose, as is done for administration in total parenteral nutrition, and in 5% dextrose in normal saline must be satisfactorily completed before this product can be conditionally approved. As previously stated the compatibility studies should be done under conditions of light and dark, refrigeration and room temperature, and in plastic and glass containers. Determination of the appropriate plasticizer should be made on solutions in plastic containers.

With regard to chemistry, the following additional information is necessary:

1. Clarification must be made as to which of the two assay procedures submitted for vitamin E and dexpanthenol will be used (section 2 of the subject submission).

2. If the vitamin E assay method practiced by is selected, full details must be provided regarding preparation of the standard, calculations, and results. Analytical laboratory reports must be submitted as well. The entire vitamin E assay procedure must be clearly described in step-wise fashion so that duplication by our laboratory personnel can be performed without having to request additional explanations and /or data.

3. Original labeling copies rather than photocopies must be submitted.

4. Samples as required by part 9 of FD Form 356 H must be submitted.

5. Validation in our laboratories of the assay procedure for some of the vitamins may be necessary.

6. In your original application, the manufacture of the drug was to be performed by However, in your resubmission of March 27, 1981, you provided an Environmental Impact Analysis Report with the explanation that Ascot Injectables is a subsidiary of who is an alternate manufacturer of the product. Please clarify your co rporate organization.

Your cooperation will be appreciated.

Sincerely yours,

/S/ 5/11/81

Solomon Sobel, M.D.
Director
Division of Metabolism and
Endocrine Drug Products, HFD-130
Food and Drug Administration

cc: NDA Orig.
HFD-130
HFD-130/LCarter;rch/5/7,11/81(9829A)

/S/

R/D init. by REastep/5/5/81; GTroendle/5/8/81
Revised by DJKertesz/5/8/81

RWP

NDA 18-439

MAR 2 1981

Ascot Hospital Pharmaceuticals, Inc.
Attention: Mr. Irving C. Udell
8050 N. Lawndale Avenue
Skokie, Illinois 60076

Gentlemen:

Please refer to your new drug application dated January 7, 1980, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act and in response to the July 13, 1979 Federal Register notice on conditions for marketing parenteral multivitamin products, for the preparation Multivitamin Concentrate for Infusion.

We also refer to your resubmission of September 23, 1980.

The manufacturing and controls requirements of the notice appearing in the Federal Register have not been fulfilled and we request that this be done promptly. In this regard items 3, 4, 8, 15, and 17 of our letter dated March 26, 1980 have not been complied with. We have the following additional comments and/or requests:

1. The statement of composition must be further revised to state the proper designation and/or grade for the ingredient "Riboflavin-5'-Sodium Phosphate". It is incorrectly stated to be USP.

2. It is stated that "Vitamin-E" is assayed according to the "AOAC" method and "Dexpanthenol" according to the
page 215. The subject methods do not state the respective specifications. Consequently, they must be submitted by you exactly as adhered to for the manufacture of the drug product. The method referred to for the biological assay of "Biotin" is shown to be a "Protein-Biological Adequacy Test" which does not measure the vitamin. An official biological assay must be submitted.

3. We note that reference is made to USP XIX and/or NF XIV regarding many of the assay procedures. Your attention is directed to the fact that USP XX and NF XV has been official since July 1, 1980.

4. The source and composition of the closure are required.

5. Actual specimens of the container labels, when available, are required rather than typewritten copies. Additionally, the container labels should be revised to show the unit of measure following the amount for each ingredient as is done in the package insert.

6. Validation by our laboratories of the analytical methods submitted, as they apply to your product may be required. This also applies to Vitamin K, content of Vial B (Pediatrics).

7. An environmental impact analysis report must be submitted for your manufacturer.

From the medical standpoint we have the following comments and requests:

1. The labeling as submitted is not satisfactory. Separate drafts for adult and pediatric preparations should be submitted. These drafts should include a warning that pyridoxine can increase the efficacy of levodopa in the treatment of parkinsonism. They should also include information on the toxicity of vitamins A and D. The adult insert should state that vitamin K is not included in the formulation and therefore supplements of it may be needed.

   The composition of the pediatric formulation for Vial A lists an incorrect amount of dexpanthenol. The AMA recommendation was 5 mg., not 50 mg.

   The word refrigerator is misspelled on the last page of the draft insert.

2. The compatibility studies as requested in our letter of March 26, 1980 must be completed before the application can be approved. Studies done by large volume parenteral manufacturers were required prior to the marketing of their products in plastic containers. They are not required to test every new product that comes onto the market for addition to their solutions.

3. A more detailed protocol for clinical studies should be submitted by the time the compatibility studies are completed. This protocol should include such details as the administration of the drug and time of drawing blood for the vitamin determinations, and an estimate of the number of subjects that would be studied short-term and long-term.

Your cooperation will be appreciated.

Sincerely yours,

/S/ 3/4/81

Solomon Sobel, M.D.
Director
Division of Metabolism and
Endocrine Drug Products, HFD-130
Food and Drug Administration

cc:
NDA Orig. ✓
HFD-130
HFD-130/LCarter;rch/2/27/81 /S/ 3/27/81

3-3-81

R/D init. by REastep/2/24/81;OAlford/2/24/81;
DJKertesz/2/26/81;GTroendle/2/27/81 /S/

RWF

NDA 18-439

MAR 26 1980

Ascot Hospital Pharmaceuticals, Inc.
Attn: Irving C. Udell
8050 N. Lawndale Avenue
Skokie, Illinois 60076

Gentlemen:

Please refer to your new drug application dated January 7, 1980, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act and in response to the July 13, 1979 Federal Register notice on conditions for marketing parenteral multivitamin products, for the preparation Multivitamin Concentrate for Infusion.

We have completed our review of this application. However, before we are able to reach a final conclusion, the following additional information pertaining to the proposed formulations, in the form of an amendment adequately organized in accordance with FD Form 356H, is necessary:

1. A revised list of articles used as components of the drug to include the component "Vitamin E (alpha tocopherol)" and to exclude the U.S.P. designation for the ingredient "Biotin" as there is no U.S.P. monograph for this ingredient.

2. The statement of composition must be revised to state the quantities of actual substances as regards thiamine, riboflavin, vitamin B_6, dexpanthenol and niacinamide used, equivalent to the quantities of the corresponding vitamins recommended in the AMA guidelines. Consistent with the statement of components the U.S.P. designation for "Biotin" should be deleted in the composition as well.

3. The grades or sources of those components not indicated as U.S.P. should be given.

4. Sampling methods or plan used for each component not indicated as U.S.P. should be given.

5. The methods of testing as well as the specifications for the components whether or not included on pages 00119 through 00140 should be submitted. If the release assay procedures required under 8(n) are those listed on pages 00205-00206, this should be stated and all acceptance specifications given unless these are

included within the references on those pages.

6. If the) is used for the assay of the vitamins, resolution data for a typical lot of your preparation should be submitted. The

7. Typical batch formulae including proposed overages should be submitted.

8. The manufacturing instructions should be in more detail to include quantities, volumes, temperatures, etc.

9. A detailed description of the container and closure.

10. An allowable numerical difference between the actual yield and the theoretical yield of the vials should be stated.

11. Data regarding the labeling process, labeling inventory and storage.

12. Sterility and pyrogen testing must be described.

13. The methods of assay used for the antioxidants/preservatives in the finished solution should be stated.

14. The stability protocol should be expanded to state light conditions.

15. Studies of adsorption of formulation components to ordinary glassware and plastic containers used in IV administration should be performed.

16. Proposed labels and labeling should be submitted.

17. Fulfillment of all sample requirements specified in item 9 of FD Form 356H must be done.

18. You must submit an environmental impact analysis report.

From the medical labeling standpoint:

1. The indications should include total parenteral nutrition.

2. Compatibility studies with TPN solutions should be done with storage up to 24 hours unless vitamin losses prior to 24 hours are such that further storage is not warranted. These studies should be conducted under conditions of light and dark unless light storage does not result in excessive losses. Each formulation should be studied for compatibility in a solution of 5% dextrose in normal saline and in two different, commonly used preparations of amino acids in 50% dextrose.

3. The pediatric formulation proposed by the AMA guidelines is designed for use in children up to the age of 11 years. The ages for testing these formulations should be adjusted accordingly.

For your information, no guidelines for doing clinical studies on these formulations will be published.

Your prompt response will be appreciated.

Sincerely yours,

/S/ 3/26/80

Solomon Sobel, M.D.
Director
Division of Metabolism and
Endocrine Drug Products
Bureau of Drugs

/S/ 3/26/80

cc: NDA Orig.
HFD-130
HFD-130/GTroendle,3/12/80
HFD-130/JGueriguian,3/13/80
HFD-130/OAlford,3/12/80
HFD-130/DKertesz,3/13/80
HFD-130/VBerliner,3/13/80
HFD-130/WIbrahim,3/11/80,3/18/80,st,3/17/80
Revised 3/24/80
R.D. init. by REastep 3/11/80

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REVIEWED/WAITING FIRM