

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

16-635

Trade Name: Cyanocobalamin Co 57 Capsules

Generic Name: Cyanocobalamin; Cyanocobalamin Co-57: Intrinsic Factor

Sponsor: Mallinckrodt

Approval Date: June 21, 1968

Indications: For the diagnosis of pernicious anemia and other conditions related to malabsorption of vitamin B12

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

16-635

APPROVAL LETTER

NDA 16-635

AF: 12-458

JUN 21 1968

Mallinckrodt Chemical Works (Mallinckrodt/Nuclear)
Attention: James A. Peterson
2703 Wagner Place
Maryland Heights, Missouri 63042

Gentlemen:

This acknowledges the receipt on May 1, 1968 of your communication dated April 29, 1968 enclosing printed labeling pursuant to your new drug application for Cyanocobalamin Co 57 Capsules.

The application was filed on May 1, 1968.

On page 8, in the first paragraph under Clinical Reports, the last sentence should read "Abnormal absorption is indicated in the 0-3% range" and not "0.3% range" as shown. This value is properly shown in the Test Procedure section under Interpretation. Since this is a simple typographical error in a non-vital portion of the labeling, we are accepting the labeling with the recommendation that the correction be made in subsequent editions of the labeling.

We have completed the review of this application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved.

The enclosures summarize the conditions relating to the approval of this application.

Please submit one market package without the drug, when available.

Sincerely yours,

Herbert L. Ley, Jr., M.D.
Director
Bureau of Medicine

Enclosures:

cc: → Orig NDA Dup Trip (KAN-DO) MD-100 MD-150
MD-300 MD-14 MD-456 MD-1 MD-8

R/D Endorsed by: HMPostman; CFBrueening 6/3/68.

HMPostman/jtm

H.M. Postman
6-4-68

6/3/68
B. J. Janczyk, MD
6/4/68

CF Brueening
6/4/68

E. R. Meyers
6/4/68

NOTICE OF APPROVAL NEW DRUG APPLICATION OR SUPPLEMENT		NDA NUMBER NDA 16-635
		DATE APPROVAL LETTER ISSUED JUN 21 1968
TO: Press Relations Staff (CE-300)	FROM: <input checked="" type="checkbox"/> Bureau of Medicine <input type="checkbox"/> Bureau of Veterinary Medicine	
ATTENTION Forward original of this form for publication only after approval letter has been issued and the date of approval has been entered above.		
TYPE OF APPLICATION <input checked="" type="checkbox"/> ORIGINAL NDA <input type="checkbox"/> SUPPLEMENT TO NDA		CATEGORY <input checked="" type="checkbox"/> HUMAN <input type="checkbox"/> VETERINARY
TRADE NAME (or other designated name) AND ESTABLISHED OR NONPROPRIETARY NAME (if any) OF DRUG Cyanocobalamin Co 57		
DOSAGE FORM Capsules		HOW DISPENSED <input checked="" type="checkbox"/> RX <input type="checkbox"/> OTC
ACTIVE INGREDIENT(S) (as declared on label. List by established or nonproprietary name(s) and include amount(s), if amount is declared on label.) Cyanocobalamin Co57		
NAME OF APPLICANT (Include City and State) Mallinckrodt Chemical Works (Mallinckrodt/Nuclear) Maryland Heights, Missouri 63042		
PRINCIPAL INDICATION OR PHARMACOLOGICAL CATEGORY Radiopharmaceutical - Diagnostic Aid		
COMPLETE FOR VETERINARY ONLY		
ANIMAL SPECIES FOR WHICH APPROVED		
COMPLETE FOR SUPPLEMENT ONLY		
CHANGE APPROVED TO PROVIDE FOR		
FORM PREPARED BY NAME Helen M. Postman		DATE
FORM APPROVED BY NAME Charles F. Bruening		DATE

**CENTER FOR DRUG EVALUATION AND
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APPLICATION NUMBER:

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LABELING

the entire body. The liver and kidney are the primary sites of accumulation. The liver is the most significant storage organ and is believed to contain about one-third to one-half of the total body content. Because cyanocobalamin is strongly bound to tissue protein, it tends to remain in the body for extended periods. The major portion is stored in five or six compartments within the body. The biological half-life of cyanocobalamin in these various compartments ranges from 9 to 1300 days.^{2, 5, 6, 14, 19} In the liver, the generally accepted biological half-life values range from 12-14 months. Elimination of cyanocobalamin from the body is ultimately achieved by urinary excretion.

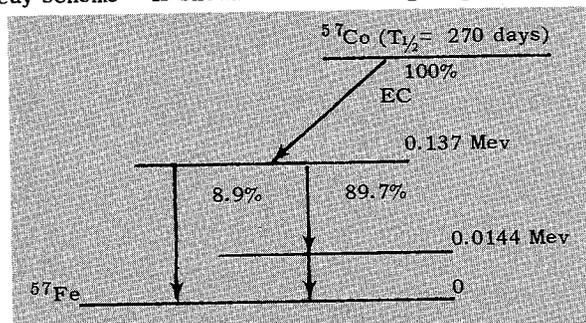
PHYSICAL CHARACTERISTICS AND RADIATION DOSIMETRY

Physical Characteristics

Decay Scheme: Cobalt-57 decays by electron capture to ^{57}Fe with a half-life of 270 days and an L/K ratio of 0.2.²¹ The process of K electron capture yields a 6.4 Kev X ray, and L electron capture results in a calculated emission of a 0.71 Kev X ray. Both X rays are treated as beta particles for dosimetry purposes.

The ^{57}Co nuclide emits a 137 Kev gamma ray in 8.9% of the disintegrations, and a 123 Kev and 14.4 Kev gamma ray in 89.7%.¹⁰ The 14.4 Kev photon undergoes internal conversion in 81.6% of the emissions, while the 123 and 137 Kev photons are internally converted 1.0% and 1.2%, respectively.¹⁰

The decay scheme²¹ is shown in the following diagram:



Specific Gamma Ray Dose Constant (Γ): The contribution of each gamma ray to the total value of the constant may be calculated from the following equation:

$$\Gamma_i = (1.5 \times 10^5) E_i N_i \{\mu_a\}_i$$

where Γ_i = contribution to Γ by γ_i in R/mCi-hr @ 1 cm.

E_i = energy of the gamma in Mev.

N_i = number of gammas of energy E_i per disintegration

$\{\mu_a\}_i$ = true linear absorption coefficient in air at energy E_i

Smith, Harris and Rohrer²⁰ have reported a value for Γ of 0.99 R/mCi-hr @ 1 cm for ^{57}Co .

Local Energy Deposition (E_β): no beta particle is emitted in the decay process. However, the low energy of the 6.4 and 0.71 Kev X rays resulting from the electron capture process are considered beta particles due to their high absorption coefficients. The other factors contributing to E_β are the orbital electrons emitted as a result of the internal conversion of the various gamma rays. The value of E_β , reported by Smith, Harris and Rohrer for ^{57}Co is 0.023 Mev.²⁰

Dosimetry

Metabolic Pathway: Rosenblum¹⁴ has reported that an oral dose of 0.5 micrograms of cyanocobalamin followed by the parenteral administration of 1 to 2 milligrams crystalline vitamin B₁₂ results in a total absorption of approximately 75%. Of this, about one-third is eliminated in the urine in the first 24 hours following ingestion. Apparently about 50% of the administered dose is thus retained in the body, which would correspond to approximately 0.25 microcurie with an oral dose of 0.5 microcurie administered. About one-third to one-half of this would be found in the liver, with the remainder distributed among other tissues and organs. In the following calculations it will be assumed that the contribution to the whole body radiation dose by the liver concentration of ^{57}Co is accounted for by using a whole body concentration of 50% of the administered dose.

The average half-time of disappearance of cyanocobalamin from the liver has been reported^{14, 19} as 11 to 14 months, with an upper extreme of 29 months.

Method of Calculation: The estimated absorbed dose in rads to the organ or area of interest is calculated from the relation

$$D_{\beta+\gamma} = C T_{\text{eff}} (73.8 E_\beta + 0.0346 \bar{\Gamma})$$

where $D_{\beta+\gamma}$ = total dose from gamma and beta components

C = concentration of the radioisotope in microcuries per gram

T_{eff} = effective half-life (days) =

$$\frac{\text{Biological Half-life } (T_b) \times \text{Physical Half-life } (T_p)}{\text{Biological Half-life } (T_b) + \text{Physical Half-life } (T_p)}$$

\bar{g} = average geometry factor for organ or area of interest

Calculated Dose to Liver:

Assume:

Mass of liver = 1700 gm

$$C = \frac{0.125}{1700} = 0.73 \times 10^{-4} \frac{\mu\text{Ci}}{\text{gm}}$$

\bar{g} = 65

T_b = 400 days

$$T_{\text{eff}} = \frac{400 \times 270}{400 + 270} = 162 \text{ days}$$

$$D_{\beta+\gamma} = (0.73 \times 10^{-4}) (162) \\ \{ 73.8 (0.023) + 0.0346 (0.99) (65) \} \\ = 0.046 \text{ rad}$$

Note - The dose computed for ^{60}Co by the same technique is 0.865 rad

Calculated Dose to Whole Body:

Assume:

$$\text{Mass of Body} = 70,000 \text{ gm}$$

$$C = \frac{0.25}{70000} = 0.358 \times 10^{-5} \frac{\mu\text{Ci}}{\text{gm}}$$

$$T_b = 1300 \text{ days}$$

$$T_{\text{eff}} = \frac{270 \times 1300}{270 + 1300} = 223 \text{ days}$$

$$\bar{g} = 125$$

$$D_{\beta+\gamma} = (0.358 \times 10^{-5}) (223) \\ \{ 73.8 (0.023) + 0.0346 (0.99) (125) \} \\ = 0.005 \text{ rad}$$

Note - The dose for ^{60}Co computed similarly is 0.174 rad

INDICATIONS

Cyanocobalamin Co^{57} has gained wide acceptance as a valuable tool in the diagnosis of pernicious anemia and other conditions related to malabsorption of vitamin B_{12} . By means of the ^{57}Co label, it is possible to determine the extent to which the vitamin is being absorbed. In contrast to other conditions resulting in a deficiency of vitamin B_{12} , including various disturbances of the gastrointestinal tract and nutritional deficiency, pernicious anemia results from the lack of gastric secretion of intrinsic factor. As a result, a differential diagnosis for pernicious anemia can be achieved by determining the extent of Cyanocobalamin Co^{57} absorption following the administration of intrinsic factor.

CONTRAINDICATIONS

Radiopharmaceuticals are contraindicated in women of child bearing capacity, during lactation, and in persons less than 18 years of age unless in the judgment of the physician the situation requires their use.

PRECAUTIONS

Radiopharmaceuticals, produced by nuclear reactor or cyclotron, should be used only by physicians who are qualified by specific training in

the use and safe handling of radioisotopes and whose experience and training have been approved by an individual agency or institution already licensed in the use of radioisotopes.

Adequate care should be taken to minimize the radiation exposure to the patient and other individuals involved in the procedure. As a general rule, the use of radiopharmaceuticals should be limited to the smallest reasonable dose to the patient consistent with the greatest value in terms of relevant diagnostic information or therapeutic effect.

To minimize the accumulation of the Cyanocobalamin Co^{57} in the liver, a flushing dose of non-radioactive cyanocobalamin is *strongly recommended*. An intramuscular dose of 1000 micrograms is normally employed for this purpose. Control samples of blood, stool, or urine should be obtained and checked for radioactivity before proceeding with the test. Any residual gamma emitting radioisotopes within the body from previous studies may affect the accuracy of the test.

Several factors are known to affect the accuracy of the urinary excretion test. Falsely low values may be obtained in the presence of renal disease. In such cases it may be advisable to extend the urine collection period to 48 hours. Some patients have also been found to be refractory to hog intrinsic factor. If the absorption of Cyanocobalamin Co^{57} is not significantly increased, i.e. to the 6% level or above with the use of hog intrinsic factor, repeating the test with human intrinsic factor is advised before ruling out a diagnosis of pernicious anemia.¹⁶ Alterations in the normal intestinal bacterial flora have also been reported to interfere with the absorption of cyanocobalamin. In such cases, the test should be repeated three to four days following a course of orally administered tetracycline or other appropriate antibiotic.²² Other factors which may affect the accuracy of the test include failure to administer a flushing dose of non-radioactive cyanocobalamin, incomplete urine collection, and ingestion of food or vitamin B_{12} within 8 hours preceding the test.¹

ADVERSE REACTIONS

Adverse reactions associated with the clinical use of Cyanocobalamin Co^{57} have not been reported.

TEST PROCEDURE

The urinary excretion (Schilling) test is by far the most frequently employed radioisotopic procedure in determining the absorption of Cyanocobalamin Co^{57} . In some instances a fecal excretion test may be required or preferred. The essential details of these test procedures are provided below. Absorption of radiocyanocobalamin has also been studied by means of external counting over the liver and determination of plasma levels.^{7, 8} However, these procedures are infrequently employed in routine clinical practice.

Urinary Excretion (Schilling) Test: The following general procedure is normally employed:

1. To determine that no interfering gamma emitting radioisotopes are present from previous studies, a control urine specimen is recommended (see Precautions). Collect a 12-hour urine specimen from approximately 7:00 P.M. of the preceding day to 7:00 A.M. of the test day. Check for radioactivity. If radioactivity is present,

repeat this procedure until none is found in the urine. This delay in performing the test due to residual radioactivity may be eliminated if appropriate instrumentation is available, such as radioisotope spectrometer, which permits the counting of specific gamma energies with the exclusion of others that may be present.

2. Administer 1 Cyanocobalamin Co57 capsule containing approximately 0.5 microcurie ^{57}Co and 0.5-0.6 microgram cyanocobalamin. The patient should have fasted for at least 8-12 hours prior to receiving the test dose. Following ingestion of the test dose, a light breakfast may be given. Normal noon and evening meals are permitted.
3. One to 2 hours later, a dose of 1000 micrograms of non-radioactive cyanocobalamin should be administered intramuscularly.
4. Collect the total urine excretion for the next 24 hours following step 2. The patient's bladder should be voided immediately prior to the administration of the test dose and at the termination of the 24 hour collection period.
5. Dilute the collected urine with water to a convenient volume, e.g. 2000 ml, using a volumetric flask.
6. Obtain an accurately measured aliquot and count in an appropriate instrument such as a well type scintillation counter for 5-15 minutes. Obtain a background count, by counting for the same length of time employed for the urine sample. Subtract the background from the sample counts to obtain the net sample counts.
7. Count a ^{57}Co standard having the identical volume and geometry as the test urine sample counted in step 6. Mallinckrodt/Nuclear Reference Standard Cobalt Co57 (Cat. No. 403) may be employed. This standard is prepared to be equivalent to 1% of the total radioactivity of a single Cyanocobalamin Co57 capsule bearing the same lot number. It is supplied in a total volume of 4 ml. If this reference standard is employed, the test urine sample aliquot (step 6) must also be 4 ml.

An alternate standard may be prepared by using a capsule containing the same amount of radioactivity (^{57}Co) as administered to the patient. This may be accomplished by thoroughly dissolving the capsule in about 50 ml of hot water. The resulting solution should be diluted to a convenient volume, e.g. 100 ml. and accurate aliquots obtained to represent a known percentage of the total administered dose. The aliquot must be diluted to the identical volume and counted under the same conditions as the test urine sample in step 6. Obtain a background count and subtract from the standard count to determine the net count for the reference standard.

8. Determine the percent of Cyanocobalamin Co57 excretion by the following:

$$\text{Percent } ^{57}\text{Co in the urine} = \frac{\text{Net urine sample CPM} \times 500}{\text{Net standard CPM} \times 100^*} \times 100$$

*This correction value is necessary if the Mallinckrodt/Nuclear 1% Reference Standard is employed. If another standard is used, the net standard count must be multiplied by the appropriate factor to obtain a value equivalent to the administered dose.

Interpretation: Generally, pernicious anemia can be ruled out if the amount of ^{57}Co found in the urine is greater than 6-10% of the administered dose. A value in the range of 0-3% normally indicates pernicious anemia or other conditions resulting in a lack of vitamin B₁₂ absorption. Results in the 3-5% range are somewhat questionable and usually require further analysis. 1, 9, 11, 12, 15, 16, 18

If a low value is obtained, the test is repeated after 48 to 72 hours, following the same procedure described above except that a dose of 60 milligrams of intrinsic factor concentrate is administered along with the Cyanocobalamin Co57. If, in the presence of intrinsic factor, the urinary excretion of ^{57}Co increased to the normal range, the diagnosis of pernicious anemia is confirmed.

Various factors may affect the accuracy and interpretation of the test. Please refer to the section under PRECAUTIONS for a discussion of these points.

Fecal Excretion Test: The extent of vitamin B₁₂ absorption can also be determined by the difference in the administered dose and the amount recovered in the feces. This test is considerably more time consuming, however, and requires a great deal more patient cooperation than the urinary excretion method.

The following general procedure is employed in conducting this test:

1. Following administration of one capsule of Cyanocobalamin Co57, collect all stools in individual containers. Stools *must not* be contaminated with urine. Continue to count each container separately until less than 1% of the dose administered is found in two successive samples. A period of 5-15 days is normally required.
2. Homogenize the combined stool samples and dilute as needed to appropriate counting volume. Determine the total radioactivity present.
3. Dilute the Mallinckrodt/Nuclear Reference Standard, or one prepared as described in step 7 under the Urinary Excretion Test, to a volume equal to the combined stool sample. Count the standard and the stool sample, correcting both values for background.
4. Determine the amount of radioactivity recovered in the stools as a percentage of the administered dose as follows:

$$\text{Percent of administered dose} = \frac{\text{Net stool sample CPM}}{\text{Net standard CPM} \times 100^*} \times 100$$

*This correction value is necessary if the Mallinckrodt/Nuclear 1% Reference Standard is employed. If another standard is used, the net standard count must be multiplied by the appropriate factor to obtain a value equivalent to the administered dose.

Interpretation: In normal patients, approximately 50% or less of the administered dose will be recovered in the feces. Patients with impaired absorption will excrete from 75-100% of the administered dose. 7,9 A diagnosis of pernicious anemia can be established in those patients who exhibit a normal absorption following a repeat study in which intrinsic factor is administered.

Dosage: For the diagnosis of pernicious anemia using either of the above two procedures, the usual dosage of Cyanocobalamin Co57 is a

single capsule containing 0.5 microcurie ^{57}Co and approximately 0.5 microgram cyanocobalamin.

CLINICAL REPORTS

Numerous reports have been published discussing the clinical use of radiocyanocobalamin, specifically Cyanocobalamin Co^{57} and Co^{60} . Of the various procedures employed to evaluate the absorption of vitamin B_{12} , the urinary excretion test developed by Schilling^{15, 16, 17, 18} is the most widely used. He has reported very satisfactory results following the general procedure previously described. Expressing the results in terms of percent of administered dose, Schilling reports normal values in the range of 7-40%. Abnormal absorption is indicated in the 0.3% range.

In a series of 624 tests, Germann¹ reported 101 cases in which excretion was 2% or less. These values were considered definitely abnormal. In those cases where the results correlated with the clinical findings, a repeat test with intrinsic factor was considered not necessary to obtain a diagnosis of pernicious anemia. Germann further reports that results in the 3-4% excretion range deserve further analysis and values of 5% and above can be considered normal.

Using the urinary excretion test of Schilling, Reisner, et al.¹² reported normal values in the 8-20% range. However, in patients with pernicious anemia, they observed essentially no excretion of radioactivity in the urine.

Several authors have reported on the fecal excretion test.^{7, 9} In patients with pernicious anemia, between 75 and 100% of the administered dose will generally be recovered in the feces. Normal patients will usually excrete less than 50% of the dose.

As reported by Nelp,⁸ an evaluation of vitamin B_{12} absorption can also be made by determining plasma levels between 8 and 14 hours following ingestion of Cyanocobalamin Co^{57} . A major advantage reported for this procedure is that unlike the Schilling test, results are not dependent upon renal function.

A fourth procedure reported by Glass, et al. is based on the measurement of hepatic uptake of radiocyanocobalamin by means of external scintillation counting.⁵ Because of the greater convenience of other procedures, the liver uptake method is not generally employed for routine use.

HOW SUPPLIED

Catalog Number

402 Cyanocobalamin Co^{57} Capsules. Each capsule contains approximately 0.5 microcurie Cyanocobalamin Co^{57} having a specific activity ranging from 0.8 to 1.0 microcurie/microgram of cyanocobalamin. It is recommended that Cyanocobalamin Co^{57} Capsules not be used after 6 months from the date of manufacturer's standardization.

RADIOACTIVE DECAY

The radioactive potency of the product is stated on the label as of a

certain date. Corrections for radioactive decay can easily be made by consulting the following table.

Cobalt-57	
Half-life = 270 days (38.57 weeks)	
Days Elapsed	Activity Remaining %
1	99.7
5	98.7
10	97.4
15	96.2
20	95.0
25	93.7
30	92.5
35	91.3
40	90.2
45	89.0
50	87.9
60	85.1
70	83.6
80	81.4
90	79.3
100	77.4
110	75.4
120	73.5
130	71.7
140	69.8
150	68.1
160	66.3
170	64.7
180	63.0

SELECTED REFERENCES

1. Germann, D. R., Cobalt 60 Tagged B_{12} As a Diagnostic Tool in the General Isotope Laboratory, *Am. J. Roent, Rad. Ther. and Nucl. Med.*, 85:59-61, 1961.
2. Glass, G. B. J., Radioactive Vitamin B_{12} in the Liver III. Hepatic Storage and Discharge of Co^{60} B_{12} in Pernicious Anemia, *J. Lab. & Clin. Med.*, 52:875, December, 1958.
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17. Schilling, R. F., Intrinsic Factor Studies. II. The Effect of Gastric Juice on the Urinary Excretion of Radioactivity After the Oral Administration of Radioactive Vitamin B₁₂, *J. Lab. and Clin. Med.*, 42:860, 1953.
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APPEARS THIS WAY ON ORIGINAL

PRINTED IN U.S.A.

ISSUED MARCH 1968

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
16-635

MEDICAL REVIEW(S)

SUPPLEMENTAL MEDICAL SUMMARY OF NDA 16-635

November 28, 1967

NDA 16-635

Sponsor: Mallinckrodt/Nuclear
Mallinckrodt Chemical Works
2703 Wagner Place
Maryland Heights, Missouri 63042

Name of Drug: Cyanocobalamin Co57
Vitamin B12 Co57

Dosage Forms and Route of Administration: Capsules for oral administration. Each capsule contains approximately 0.5 microcuries cyanocobalamin Co57 having a specific activity ranging from 0.8 to 1.0 microcurie/microgram of cyanocobalamin.

Category or Use of Drug: Radiopharmaceutical for the diagnosis of pernicious anemia and Vitamin B12 malabsorption syndromes.

Material Reviewed: NDA 16-635
NDA 16-634 This is the same drug labeled with Co60.

Chemist's Summary: Aug. 22, 1967. Incomplete 505(b)(2) (3).

Pharmacologist's Summary: June 1, 1967 Incomplete 505(b)(1).

Medical Officer Review Original: May 24, 1967. Incomplete 505(b)(6) labeling.

Most of the above deficiencies were discussed with the company representatives during a conference on July 6, 1967. Final chemist's summary was waiting on a factory inspection report.

Incomplete letter issued on October 4, 1967.

This review acknowledges receipt of supplemental information on November 8, 1967 which contains additional data requested during the above mentioned conference and the incomplete letter. Only the items pertinent to the medical review are discussed.

All of the suggested changes and recommendation have been made in the new proposed labeling. However, there appears to be a typographical error in the dosimetry section of 16-635. The radiation dose to the liver from 57Co should read 0.046 rad instead of the 0.0046 rad as shown.

Since the original review and conference on this product it has been brought to our attention that certain intestinal flora may invalidate the Schilling Test and that the test may need to be repeated after a course of tetracycline therapy. (Scudmore, H. H., et. a.: Diverticulosis of the Small Intestine and Macrocytic Anemia with the Report of Two Cases and Studies on Absorption of Radioactive Vitamin B12. Gastroenterology 34:66 1958.) We suggest that this information be incorporated in the text of the labeling.

In keeping with the above suggestion, it is further recommended that the several clinical situations which may invalidate the test be more prominently emphasized by including them under the PRECAUTIONS section in both submissions. These include the following:

1. The substitution of human intrinsic factor in persons who have become unreactive or sensitive to hog intrinsic factor.
2. Persons with impaired renal function may require 48 or 72 hour urine collections. When creatinine clearance is below 40 ml per minute, urinary excretion of vitamin B12 may be abnormally low.
3. Abnormal intestinal flora may invalidate the test and require a course of tetracycline therapy.

Recommendations: If the company will submit a letter of agreement, that the above mentioned changes will be made in the final printed label, I recommend that this submission be accepted as complete.

Bryant L. Jones, M.D.
Bryant L. Jones, M.D.

cc:

~~Orig IND~~

Dup

Trip (SL)

M-100

M-150

M-300

BLJones/jtm 12/4/67

MEDICAL OFFICER REVIEW OF NDA 16-635

Original

May 26, 1967

Sponsor: Mallinckrodt Nuclear
Mallinckrodt Chemical Works
2703 Wagner Place
Maryland Heights, Missouri 63042

Name of Drug: Cyanocobalamin Co57
Vitamin B₁₂ Co57

Dosage Forms and Route of Administration: Capsules for oral administration. Each capsule contains approximately 0.5 microcuries cyanocobalamin Co57 having a specific activity ranging from 0.8 to 1.0 microcurie/microgram of cyanocobalamin.

Category or Use of Drug: Radiopharmaceutical for the diagnosis of pernicious anemia and vitamin B₁₂ malabsorption syndromes.

Material Reviewed: NDA 16-635
NDA 16-634 This is the same drug labeled with Co60.

Chemist's Summary: Still under review.

Pharmacologist's Summary: Still under review.

Clinical Evaluation: These capsules are to be used in a diagnostic procedure. Radioactive vitamin B₁₂ provided the only way to confirm the diagnosis of pernicious anemia in patients who are receiving B₁₂ therapy and of diagnosing sub-acute combined degeneration of nerves in patients who have received folic acid treatment and are no longer anemic. It offers a differential diagnosis of Sprue and other vitamin B₁₂ malabsorption syndromes.

Review of Studies Supporting Safety and Efficacy: Case reports on a total of 26 patients are provided from Dr. (b)(4)

(b)(4) The Schilling urinary test was used utilizing 0.5 uCi capsules of cyanocobalamin. Pernicious anemia was diagnosed on one case. No untoward reactions were reported.

Since this procedure has been in extensive use for about ten years, selected reports from the literature summarizing results of clinical studies by several investigators are included. Reprints of these papers and accurate abstracts have been included and made a part of this submission. Each reprint and abstract has been carefully checked for accuracy and content and each found to be well selected and complete. Inclusion of an abstract of each reference in this review is not indicated. No known reports have been omitted which would bias the evaluation of the safety and effectiveness of this drug.

Review of Labeling: The label for this drug is comprehensive, balanced, and complete. It follows the suggested outline for radiopharmaceutical drugs. However, I feel that there are some minor errors of interpretation and presentation which should be corrected. These errors are relatively minor and need not prejudice the submission. The points are as follows:

1. Under Dosimetry.

(b)(4)

(b)(4)

2. In paragraph 2 under Dosimetry. The references (20,21) seem to be in error. I believe this reference should be 19. I also believe that reference 20 is not germane to this work.
3. The proper symbol for average geometry factor is lower case g bar (\bar{g}).

Conclusions:

1. Cyanocobalamin Co57 capsules of 0.5 uCi strength are safe and efficacious for the purpose as stated in the package insert.
2. This radiopharmaceutical is not on my list of isotopes considered to be "well-established" by the AEC but its qualities have been clearly demonstrated to be safer than Co60 which does appear on the list.

Recommendations: When the editorial corrections of the package insert have been made, I recommend that this NDA 16-635 be accepted as complete for filing under the Act.

cc:
Dup NDA
Trip NDA (SL)
OND DOR ODS
BLJones/mm
5/29/67

Bryant L. Jones, M.D.
Bryant L. Jones, M.D.

MEDICAL OFFICERS SUMMARY OF NDAs 16-634 and 16-635

Sponsor: Mallinckrodt/Nuclear
Mallinckrodt Chemical Works
2703 Wagner Place
Maryland Heights, Missouri 63042

Name of Drug: Cyanocobalamin Co 60
Vitamin B₁₂ Co 60

Medical Review: May 24, 1967 Incomplete 505(b)(6) labeling.
November 28, 1967 Incomplete labeling but could be complete
if minor changes in final printed labeling could be made.

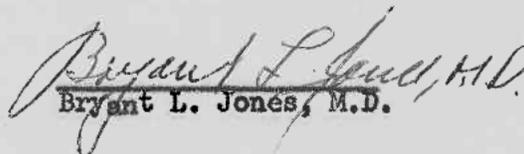
This review acknowledges receipt of revised labeling which incorporates the suggestions as discussed in phone conversation of November 30, 1967.

All of the suggested changes have been made.

The supplement also contains manufacturing data which does not concern this medical review.

Resume & Evaluation: The submission contains all the information necessary for a practitioner to use this drug safely and efficaciously.

Recommendations: I recommend that this submission be accepted as complete.


Bryant L. Jones, M.D.

cc:
~~Orig NDA~~
Dup
Trip
M-100
M-150
M-300
BLJones/jtm 12/22/67

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

16-635

CHEMISTRY REVIEW(S)

CHEMIST REVIEW NOTES

Division of Oncology and Radiopharmaceuticals

- I. NDA: 16-635 January 11, 1968
PROPRIETARY NAME: Cyanocobalamin Co-57 Mallinckrodt Chem. Works
DOSAGE FORM: Capsule (Oral), Rx Mallinckrodt/Nuclear
Maryland Heights, Mo.
- II. CHEMICAL INFORMATION:
FAMILY: Radiopharmaceutical
RELATED MFs, NDAs, IND: MF 998 (Mallinckrodt); MF ^{(b)(4)} ;
^{(b)(4)} ; NDA 6668 (Merck);
IND 3934 (Mallinckrodt)
- III. PREVIOUS SUMMARY AND LETTER: (a) Chem. Summary - Aug. 18, 1967
(b) Inc. letter to applicant, Oct. 4, 1967;
Inc. 505(b)(2)(3) and (4).
RESUBMISSION (AMENDMENTS) REVIEWED: (a) Amendment Nov. 7, 1967 ---
mfg. info. and labeling;
(b) Amendment Dec. 11, 1967 ---
stability, data and labeling.
- IV. a) REMARKS: Inadequacies in manufacturing information in NDA have been
corrected by additions and revisions. Stability has not been
a problem; data to continue to be submitted. Article is USP
drug.
b) CONCLUSIONS: Recommend approval.


Robert W. Jennings, Chemist

cc:
~~Orig NDA~~
Dup
Trip (KAN DO)
M-100
M-150
M-300
RWJennings/jtm 1/12/68
R/D Endorsed by: CFBruening 1/11/68

CHEMIST REVIEW NOTES

Division of Oncology and Radiopharmaceuticals

I. NDA: 16-635

August 18, 1967

PROPRIETARY NAME: Cyanocobalamin Co 57
(0.5 microcurie and
0.5-0.6 microgram)

Mallinckrodt Chem. Works
Mallinckrodt/Nuclear
Maryland Heights, Missouri

DOSAGE FORM: Capsule (Oral)
Rx

II. CHEMICAL INFORMATION:

FAMILY OR RELATED DRUGS: Radiopharmaceutical

RELATED NDA, IND, MF: Mallinckrodt IND 3934; Mallinckrodt MF 998;
(b)(4) MF (b)(4); Merck NDA 6668. (Note: If authorized -- (b)(4)
(b)(4))

III. ORIG. SUB.: Dated 4/7/67; Radiopharmaceutical diagnostic.

IV. a) REMARKS: USP Drug

NDA incomplete (b)(2),(3) ... Components/composition; capsule information needed.

NDA incomplete (b)(4) ... Need authority for full reference to MF (b)(4) which is supported in part by manufacturing information in (b)(4) NDA.

NDA incomplete (b)(4) ... Lack of stability data.

No response received to verbal comments made to applicant 7/6/67.

b) CONCLUSIONS: Original Application ... Incomplete 505(b)(2),(3) and (4).


Robert W. Jennings, Chemist

cc:

Dup NDA

Trip

M-100

M-160

ODS

R/D Endorsed by: CFBruening 8/22/67

RWJennings/jtm 8/22/67

CHEMIST REVIEW NOTES

NDA: 16-635

1. Components & Composition:

(b) (4)

2. Facilities & Personnel: EI requested.

3. Synthesis:

(b) (4)

4. Raw Material Controls:

(b) (4)

5. Other Firms:

(b) (4)

6. Manufacturing & Processing: Passable.

7. Container: Satisfactory, if stability data is passable, when received.

8. Packaging & Labeling: Satisfactory.

9. Laboratory Controls: Need authority for full reference to MF (b) (4).

10. Stability: None submitted - needed - NDA indicates studies in progress.

11. Control Numbers: Satisfactory.

12. Samples & Results: Waived; Radiopharmaceutical

(Continued from previous page)

13. Labeling: Satisfactory (controls); see MD review.
14. Establishment Inspection: Requested July 20, 1967
15. Registration: Satisfactory.

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

16-635

PHARMACOLOGY REVIEW(S)

SUPPLEMENTAL PHARMACOLOGICAL REVIEW OF NDA 16-635

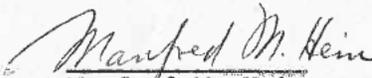
January 15, 1968

Sponsor: Mallinckrodt Chemical Works
Mallinckrodt/Nuclear

Name of Drug: Cyanocobalamin Co-57 Capsules

This NDA has been reviewed for Pharmacology on May 31, 1967 (M. M. Hein). Our objections to approval have been attended to in submissions of Dec. 11, 1967 and Nov. 7, 1967 and we have no objection to the approval of the NDA at this time.

The package insert in our judgement now supplies adequate information for use by the physician for administration of the agent in a safe, effective and judicious manner


Manfred M. Hein

cc:

~~Orig NDA~~

Dup

Trip (KAN D)

M-100

M-150

M-300

R/D Endorsed by: DJRichman 1/16/68

MMHein/jtm 1/16/68

PHARMACOLOGIST REVIEW OF NDA 16-634, NDA 16-635, IND 3934

Original

May 31, 1967

Sponsor: Mallinckrodt Chem. Works (Mallinckrodt/Nuclear)

Name of Drug: Cyanocobalamin labelled with Co⁵⁷ (NDA 16-635)
Cyanocobalamin labelled with Co⁶⁰ (NDA 16-634)
Cyanocobalamin labelled with Co⁵⁷ (IND 3934)

Cyanocobalamin is also known as Vitamin B₁₂.

Category: Radiopharmaceutical diagnostic agent.

Composition: Capsules containing

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Products are at times marketed in the form of a kit which contains the above described capsules as well as a solution of cyanocobalamin for injection (non-radioactive) and oral preparations of intrinsic factor. It is presumed that this NDA covers only the capsules.

Related MF: (b) (4); 998

Related NDA's: There are similar products by (b) (4); 14-085 (capsules); 14-086 (solution); and Squibb (NDA 16-089 (caps), and NDA 16-090 (capsules)). For radioactive cyanocobalamin under the trade names of Racobalamin 57 and Rubratope 57 and Rubratope 60. NDA 11-510 (Abbott) covers a kit for Racobalamin 60.

In addition there are about 75 NDA's which contain cyanocobalamin without the radioactive label.

IND 3934 (Mallinckrodt) is also for Radioactive Cyanocobalamin labelled with Co⁵⁷ but contains no additional information. There are also a few other non-radioactive IND's.

Clinical Indications: Product is used as a diagnostic agent to test the ability of patients to absorb Cyanocobalamin from the intestinal tract with and without the presence of exogenous intrinsic factor.

A determination of orally administered absorption of the drug substance is made by:

- 1) Measuring the radioactivity excreted in 24 hrs (Schilling test).
- 2) Measurement of the plasma level of radioactivity several hours after injection.
- 3) Measurement of the radioactivity accumulating in the liver by means of skin surface counting over the liver.
- 4) Measurement of the cumulative excretion in the stool of the radioactivity over a period of several days.

NDA 16-634
NDA 16-635
IND 3934

-2-

The first is the most popular, easiest and reliable and has been in use for 10-15 yrs, during which probably thousands of patients have been tested. Usefulness extends to the detection of sprue, pernicious anemia, linitus plastica, malabsorption syndrome, and gastrectomy. In combination with history (to rule out gastrectomy) the use of the repeat study with intrinsic factor is said to be a positive identification method for pernicious anemia. Thus, two tests may be done in a relatively short time. Since here the material is not absorbed except in the second situation to any appreciable extent this does not double the radioactive exposure dose. A "flushing dose" of about 1000 micrograms of non-radioactive cyanocobalamin about 2 hrs after oral administration of the test dose is given IV as part of the Schilling test. Cyanocobalamin labelled with Co⁵⁷ or Co⁶⁰ is also used to evaluate hyperchromic anemias characterised by bone marrow megaloblastosis in hematology, to determine glomerular filtration rate by the renal service, and as a diagnostic procedure in which combined systemic disease is suspected by the neurology and neurosurgery disciplines. Here the injectable form is used almost exclusively and thus not subject of the NDA.

Toxicity:

Chemical

Sponsor claims safety on the basis of long time therapeutic use of Cyanocobalamin at 15-100 microgram parenterally (this is no safety test when 1000 micrograms are given as a flushing dose). A statement by Goodman and Gilman in their text: Pharmacological Basis of Therapeutics, second edition, p 1491 is quoted as follows: "Toxic side effects from the clinical use of crystalline Vitamin B₁₂ have not been reported." The 3rd edition essentially repeats this statement.

Experiments to determine the biological $\frac{1}{2}$ life in the principal target organ (liver) suggest a mean $\frac{1}{2}$ life of 8.6-11.4 months with a range from 4.7-20.8 mths in human controls. A slightly longer half life was found in pernicious anemia patients under treatment (range 4.9-29.4 mths). In these experiments the radioactivity over the liver was measured.

When transported through the blood cyanocobalamin is bound to glycoproteins and may be detected there with a $\frac{1}{2}$ life of 690 days following injection. Following an initial complex rapid phase lasting for 60-80 d a slow phase occurs in the disappearance rate of the isotope from the plasma. RBC also show an overall radioactive cyanocobalamin disappearance pattern in vivo similar to that of plasma. Thus it appears that the liver may serve as a reservoir for plasma and RBC bound cyanocobalamin since their biological life time in the blood is less than that stated.

The total body cyanocobalamin on the average is estimated at 2.5 mg. Of this about 1.3 micrograms are excreted in the urine or feces daily and needs replenishment from dietary or intestinal bacterial sources.

Cyanocobalamin with the radioactive label is produced by culture in the radioactive Co containing solution of (b) (4)

Evidence is presented to show that the radioactive content of the liver is due to cyanocobalamin labelled with Co and not deposits of other Co containing materials resulting after degradation of the molecule.

Radioactive Toxicity

Co is an integral part of the cyanocobalamin molecule. The vitamin has been tagged with C¹⁴, P³², and H³ but the availability of various Co isotopes makes this a convenient route. The isotopes of Co are numerous and include with radiation energies and 1/2 life values: (From USPHS Radiological Handbook)

	<u>1/2 life</u>	<u>B⁺ MEV and % if data available</u>	<u>Gamma MEV and % if data available</u>
Co ⁵⁴	0.18 sec		
Co ⁵⁵	18 hrs	1.5	.247, .253, .477 and 1.41
Co ⁵⁶	77 days	.44, 1.53	.845, 0.98, 1.03, 1.22, 1.35, 1.76, 2.02, 2.56, 2.98, 3.25, and 3.47
Co ⁵⁷	267 days	none (.32 bremsstrahlung)	.014, 0.12, 0.136
Co ^{58m}	9 hrs	none	.025
Co ⁵⁸	72 days	0.47 (14.5%)	.81, 1.62
Co ⁵⁹	STABLE		

	<u>1/2 life</u>	<u>B⁻ MEV and % if data available</u>	<u>Gamma MEV and % if data available</u>
Co ^{60m}	10.47 min	1.28, 1.35, 1.56	.056, .059
Co ⁶⁰	5.27 yrs	0.312 (100%)	
Co ⁶¹	1.65 hrs	1.48 (.01%) 1.22 (95%) 1.42 (55%) 1.00 (45%)	1.173, 1.33, 2.158
Co ⁶²	1.6 or 1.4 min	0.88 (25%) 2.88 (75%)	.072
Co ⁶⁴	about 5 min		1.17, 1.47, 1.74, 2.03, 2.5

NDA 16-634
NDA 16-635
IND 3934

-4-

As this product needs to be produced biologically before use the only significant, useful "labels" are Co⁵⁶, Co⁵⁷, Co⁵⁸, Co⁶⁰. Co⁵⁸ is used in Europe but not in the U.S. Co⁵⁶ offers no advantages over Co⁵⁸ and has a much stronger gamma emission. It is not commercially available in the US or abroad. The very strong gamma radiation from Co⁶⁰, the significant beta decay and longer half life make this a poorer choice than Co⁵⁸ and Co⁵⁷. According to the tables in "Radioactive Pharmaceuticals (AEC publ. 1966 P. 459) the relative dose to the liver (critical organ)/MPC (maximum permissible concentration in the body assuming this to be 10 uCi for Co⁶⁰, 30 uCi for Co⁵⁸, and 200 uCi for Co⁵⁷) is 29, 2.3, and 1 for Co⁶⁰, Co⁵⁸, and Co⁵⁷ and the effective $\frac{1}{2}$ life in the liver calculates in days to 331, 60 and 161 days assuming a biological $\frac{1}{2}$ life of 400 d.

Evaluation and Comment: The subject of these two NDA's are 2 capsule preparations of cyanocobalamin for use as a radioactive diagnostic agent.

There is no known chemical toxicity from these products and the concomitant radiation exposure is the principal concern. Similar products by other manufacturers have had effective NDA's and were marketed since June 10, 1959 (Co⁶⁰ Vit B₁₂ by Abbott NDA #11-510 is a kit with capsules) and Aug. 8, 1963 for the other Abbott Co⁵⁷ preparations with no reported adverse reactions to date. The chemical and radioactive doses of the Abbott and Squibb products is similar to that of the subject NDA's. By the sponsor's own admission and from other sources, information is available to indicate that Co⁶⁰ delivers about 26-29 x the radiation exposure to the patient, has a significant beta radiation, a more complex radiation decay spectrum and a longer physical half life. Co⁶⁰ labelled cyanocobalamin is definitely a less favorable product. Its principal claim for use seems to be its long use by investigators who may not want to change to Co⁵⁷ and possibly the identification of radiation from separate tests where Co⁵⁷ was given at one time and Co⁶⁰ as a confirmatory test later. These seem slim reasons for approving Co⁶⁰ when Co⁵⁷ labelled cyanocobalamin is a decidedly safer and otherwise equally effective product. Indeed Co⁵⁸ Cyanocobalamin may be even more preferable but it has not been made available to date in the US. The strong gamma and the beta radiation from Co⁶⁰ also suggests that the molecule of cyanocobalamin may be subject to more internal derangement and deterioration (resulting in less accurate tests) due to self absorption as is discussed in the AEC book on radioactive pharmaceuticals. The testing for purity and standardization would also seem easier with Co⁵⁸ and Co⁵⁷ than Co⁶⁰ due to fewer radioactive decay species.

Regarding the submitted application for Co⁵⁷ cyanocobalamin NDA 16-635, there are a few points that should be modified. The label reads "Do not use after six months from date of standardization." As a user may standardize his own material, this statement bypasses the purpose intended. Expiration date should refer to 6 months after factory standardization. (Page 1, 10 of brochure and labels).

NDA 16-634
NDA 16-635
IND 3934

-5-

In line with this it seems superfluous to carry a decay table beyond the 6 months period (see page 11 of brochure).

The wording regarding the use of a flushing dose on page 5 under the heading PRECAUTIONS may be made stronger by the insertion of "strongly" recommended.

The second paragraph under Physical Characteristics and radiation dosimetry on p2 of brochure refers to "The ^{57}Fe nuclide emits ... " Should this be Co^{57} ? Sponsor should inform us as to whether this application is for the capsule form only or also encompasses the use of the "kit" which includes a standard, intrinsic factor and a flushing dose formulation of the non-radioactive drug. In the later case we would reserve the right to review the applications regarding these products.

Regarding NDA 16-634, cyanocobalamin with Co^{60} label, we should insist that the sponsor change in his package insert page 1 the words (b)(4)

The comments regarding standardization in the label and package insert as well as comments regarding flushing dose (p 5) apply equally here. Sponsor should state if the NDA is to apply to the capsules only or also to the kit.

We feel NDA 16-635 is approvable pending proper labelling. In regards to NDA 16-634 (Co^{60} labelled cyanocobalamin), we have certain reservations stated above which should be resolved. NDA 16-634 should be considered "incomplete" under section 505(b)(1) till these questions are resolved.

Manfred M. Hein
Manfred M. Hein

cc:
NDA 16-634 (Orig; Dup; Trip)
NDA 16-635 (Orig; Dup; Trip)
IND 3934 (Orig; Dup; Trip)
OND DOR ODS
MMHein/mm
R/D init. by: DJRichman
6/1/67

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

16-635

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

NDA 16 635

APR 24 1967

Mallinckrodt Chemical Works (Mallinckrodt/ Nuclear)
2703 Wagner Place
Maryland Heights, Missouri 63042

Gentlemen:

We acknowledge the receipt of your new drug application submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of drug: Cyanocobalamin Co57 Capsules

Date of application: April 7, 1967

Date of receipt: April 12, 1967

We will correspond with you further after we have had the opportunity to study the application.

Please identify any communications concerning this application with the NDA number shown above.

Sincerely yours,

Earl L. Meyers, Ph. D.
Acting Director
Division of Oncology and Radio-
pharmaceuticals
Office of New Drugs
Bureau of Medicine

SL

Dup

Trip

MED

ELMeyers

Jht/4-20-67

ACK

M. L. Wills

Form Approved
FD-356 Bureau No. 57-R003.3
NEW DRUG APPLICATION

NEW DRUG APPLICATION
ORIGINAL OR SUPPLEMENTAL
APPLICATION

Name of applicant Mallinckrodt Chemical Works (Mallinckrodt/Nuclear)
Address 2703 Wagner Place, Maryland Heights, Missouri 63042
Date April 7, 1967
Name of new drug Cyanocobalamin Co57 Capsules
(If this is a supplemental application, see Item (8))

To the Secretary of Health, Education, and Welfare,
For the Commissioner of Food and Drugs,
Washington 25, D. C.

Dear Sir:
The undersigned Mallinckrodt Chemical Works, submits this application with respect to a new drug pursuant to section 505 (b) of the Federal Food, Drug, and Cosmetic Act.

Attached hereto, in triplicate, and constituting a part of this application are the following:

1. Full reports of investigations that have been made to show whether or not the drug is safe for use and effective in use.

a. An application may be refused unless it contains full reports of adequate tests by all methods reasonably applicable to show whether or not the drug is safe and effective for use as suggested in the proposed labeling and includes all the following:

i. Detailed reports of the preclinical investigations, including studies made on laboratory animals, in which the methods used and the results obtained are clearly set forth. Such information should include identification of the person who conducted each investigation, a statement of where the investigations were conducted, and where the underlying data are available for inspection. The animal studies may not be considered adequate unless they give proper attention to the conditions of use recommended in the proposed labeling for the drug such as, for example, whether the drug is for short- or long-term administration or whether it is to be used in infants, children, pregnant women, or premenopausal women.

ii. Reports of all clinical tests sponsored by the applicant or received or otherwise obtained by the applicant should be attached. These reports should include adequate information concerning each subject treated with the drug or employed as a control, including age, sex, conditions treated, dosage, frequency of administration of the drug, results of all relevant clinical observations and laboratory examinations made, full information concerning any other treatment given previously or concurrently, and a full statement of adverse effects and useful results observed, together with an opinion as to whether such effects or results are attributable to the drug under investigation and a statement of where the underlying data are available for inspection. Ordinarily, the reports of clinical studies will not be regarded as adequate unless they include reports from more than one independent, competent investigator who maintain adequate case histories of an adequate number of subjects, designed to record observations and

permit evaluation of any and all discernible effects attributable to the drug in each individual treated and comparable records on any individuals employed as controls. Except when the disease for which the drug is being tested occurs with such infrequency in the United States as to make testing impractical, some of the investigations should be performed by competent investigators within the United States.

iii. All information pertinent to an evaluation of the safety and effectiveness of the drug received or otherwise obtained by the applicant from any source, including information derived from other investigations or commercial marketing (for example, outside the United States), or reports in the scientific literature, involving the drug that is the subject of the application or pertinent information about any relevantly related drug. An adequate summary may be acceptable in lieu of a reprint of a published article which only supports other data submitted. Include any evaluation of the safety or effectiveness of the drug that has been made by the applicant's medical department, expert committee, or consultants.

iv. If the drug is a combination of previously investigated or marketed drugs an adequate summary of pre-existing information from preclinical and clinical investigation and experience with its components, including all reports received or otherwise obtained by the applicant suggesting side effects, contraindications, and ineffectiveness in use of such components. Such summary should include an adequate bibliography of publications about the components and may incorporate by reference information concerning such components previously submitted by the applicant to the Food and Drug Administration.

b. An application may be refused unless it includes substantial evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it pur-

ports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling.

c. The complete composition and/or method of manufacture of the new drug used in each submitted report of investigation should be shown to the extent necessary to establish its identity, strength, quality, and purity if it differs from the description in item 2, 3, or 4 of the application in any way that would bias an evaluation of the report.

d. An application shall include a complete list of the names and post office addresses of all investigators who received the drug. (This may be incorporated in whole or in part by reference to information submitted under the provisions of § 130.3.)

e. Explain any omission of reports from any investigator to whom the investigational drug has been made available. The unexplained omission of any reports of investigations made with the new drug by the applicant, or submitted to him by an investigator, or the unexplained omission of any pertinent reports of investigations or clinical experience received or otherwise obtained by the applicant from published literature or other sources, that would bias an evaluation of the safety of the drug or its effectiveness in use constitutes grounds for the refusal or withdrawal of the approval of an application.

2. A full list of the articles used as components of the drug. This list should include all substances used in the synthesis, extraction, or other method of preparation of any new-drug substance, and in the preparation of the finished dosage form, regardless of whether they undergo chemical change or are removed in the process. Each substance should be identified by its established name, if any, or complete chemical name, using structural formulas when necessary for specific identification. If any proprietary preparation is used as a component, the proprietary name should be followed by a complete quantitative statement of composition. Reasonable alternatives for any listed substance may be specified.

3. A full statement of the composition of the drug. The statement shall set forth the name and amount of each ingredient, whether active or not, contained in a stated quantity of the drug in the form in which it is to be distributed, as for example, amount per tablet or per milliliter, and a batch formula representative of that to be employed for the manufacture of the finished dosage form. All components should be included in the batch formula regardless of whether they appear in the finished product. Any calculated excess of an ingredient over the label declaration should be designated as such and percent excess shown. Reasonable variations may be specified.

4. A full description of the methods used in, and the facilities and controls used for, the manufacture, processing and packing of the drug. Included in this description should be full information with respect to any new-drug substance and to the new-drug dosage form as follows, in sufficient detail to permit evaluation of the adequacy of the described methods of manufacture, processing, and packing and the described facilities and controls to determine and preserve the identity, strength, quality, and purity of the drug:

a. A description of the physical facilities including building and equipment used in manufacturing, processing, packaging labeling, storage, and control operations.

b. A description of the qualifications, including educational background and experience, of the technical and professional personnel who are responsible for assuring that the drug has the safety, identity, strength, quality, and

purity it purports or is represented to possess, and a statement of their responsibilities.

c. The methods used in the synthesis, extraction, isolation, or purification of any new-drug substance. When the specifications and controls applied to such substance are inadequate in themselves to determine its identity, strength, quality, and purity, the methods should be described in sufficient detail, including quantities used, times, temperatures, pH, solvents, etc., to determine these characteristics. Alternative methods or variations in methods within reasonable limits that do not affect such characteristics of the substance may be specified.

d. Precautions to assure proper identity, strength, quality, and purity of the raw materials, whether active or not, including the specifications for acceptance and methods of testing for each lot of raw material.

e. Whether or not each lot of raw materials is given a serial number to identify it, and the use made of such numbers in subsequent plant operations.

f. If the applicant does not himself perform all the manufacturing, processing, packaging, labeling, and control operations for any new-drug substance or the new-drug dosage form, his statement identifying each person who will perform any part of such operations and designating the part; and a signed statement from each such person fully describing, directly or by reference, the methods, facilities, and controls in his part of the operation.

g. Method of preparation of the master formula records and individual batch records and manner in which these records are used.

h. The instructions used in the manufacturing, processing, packaging, and labeling of each dosage form of the new-drug, including any special precautions observed in the operations.

i. Adequate information with respect to the characteristics of and the test methods employed for the container, closure, or other component parts of the drug package to assure their suitability for the intended use.

j. Number of individuals checking weight or volume of each individual ingredient entering into each batch of the drug.

k. Whether or not the total weight or volume of each batch is determined at any stage of the manufacturing process subsequent to making up a batch according to the formula card and if so at what stage and by whom it is done.

l. Precautions to check the actual package yield produced from a batch of the drug with the theoretical yield. This should include a description of the accounting for such items as discards, breakage, etc., and the criteria used in accepting or rejecting batches of drugs in the event of an unexplained discrepancy.

m. Precautions to assure that each lot of the drug is packaged with the proper label and labeling, including provisions for labeling, storage, and inventory control.

n. The analytical controls used during the various stages of the manufacturing, processing, packaging, and labeling of the drug, including a detailed description of the collection of samples and the analytical procedures to which they are subjected. The analytical procedures should be capable of determining the active components within a reasonable degree of accuracy and of assuring the identity of such components. If the article is one that is represented to be sterile, the same information with regard to the manufacturing, processing, packaging, and the collection of samples of the drug should be given for sterility controls. Include the standards used for acceptance of each lot of the finished drug.

o. An explanation of the exact significance of any batch control numbers used in the manufacturing, processing, packaging, and labeling of the drug, including such control numbers that may appear on the label of the finished article. State whether these numbers enable determination of the complete manufacturing history of the product. Describe any methods used to permit determination of the distribution of any batch if its recall is required.

p. A complete description of, and data derived from, studies of the stability of the drug, including information showing the suitability of the analytical methods used. Describe any additional stability studies underway or contemplated. Stability data should be submitted for any new-drug substance, for the finished dosage form of the drug in the container including a multiple-dose container in which it is to be marketed, and if it is to be put into solution at the time of dispensing, for the solution prepared as directed. If the data indicate that an expiration date is needed to preserve the identity, strength, quality, and purity of the drug until it is used, a statement of an expiration date.

q. Additional procedures employed which are designed to prevent contamination and otherwise assure proper control of the product.

(An application may be refused unless it includes adequate information showing that the methods used in, and the facilities and controls used for, the manufacturing, processing, and packaging of the drug are adequate to preserve its identity, strength, quality and purity in conformity with good manufacturing practice and identifies each establishment, showing the location of the plant conducting these operations.)

5. Samples of the drug and articles used as components, as follows:

a. The following samples shall be submitted with the application or as soon thereafter as they become available. Each sample shall consist of four identical, separately packaged subdivisions, each containing at least three times the amount required to perform the laboratory test procedures described in the application to determine compliance with its control specifications for identity and assays:

i. A representative sample or samples of the finished dosage form(s) proposed in the application and employed in the clinical investigations and a representative sample or samples of each new-drug substance, as defined in § 130.1(g), from the batch(es) employed in the production of such dosage form(s).

ii. A representative sample or samples of finished market packages of each dosage form of the drug prepared for initial marketing, and if any such sample is not from a commercial-scale production batch, in addition such a sample from a representative commercial-scale production batch; and a representative sample or samples of each new-drug substance as defined in § 130.1(g), from the batch(es) employed in the production of such dosage form(s). *Provided, however,* That in the case of medicated feeds marketed in large packages the sample should contain only three times a sufficient quantity of the medicated feed to allow for performing the control tests for drug identity and assays.

iii. A sample or samples of any reference standard and blank used in the procedures described in the application for assaying each new-drug substance and other assayed components of the finished drug; *Provided, however,* That samples of reference standards recognized in the official United States Pharmacopeia or The National Formulary

need not be submitted unless requested.

b. Additional samples shall be submitted on request.

c. Each of the samples submitted shall be appropriately packaged and labeled to preserve its characteristics; to identify the material and the quantity in each subdivision of the sample, and to identify each subdivision with the name of the applicant and the new-drug application to which it relates.

d. There shall be included a full list of the samples submitted pursuant to item 5a; a statement of the additional samples that will be submitted as soon as available; and, with respect to each sample submitted, full information with respect to its identity, the origin of any new-drug substance contained therein (including in the case of new-drug substances, a statement whether it was produced on a laboratory, pilot-plant, or full-production scale) and detailed results of all laboratory tests made to determine the identity, strength, quality, and purity of the batch represented by the sample, including assays. Include for any reference standard a complete description of its preparation and the results of all laboratory tests on it. If the test methods used differed from those described in the application, full details of the methods employed in obtaining the reported results shall be submitted.

e. The requirements of item 5a may be waived in whole or in part on request of the applicant or otherwise when any such samples are not necessary.

6. Each copy of the application shall contain three copies of each label and all other labeling to be used for the drug.

a. Each label, or other labeling, should be clearly identified to show its position on, or the manner in which it accompanies, the market package.

b. The labeling on or within the retail package should include adequate directions for use by the layman under all the conditions for which the drug is intended for lay use, or is to be prescribed, recommended, or suggested in any labeling or advertising sponsored by or on behalf of the applicant and directed to laymen.

c. If the drug is limited in its labeling to use under the professional supervision of a practitioner licensed by law to administer it, its labeling should bear information for use under which such practitioners can use the drug for use under which such practitioners can use the drug for the purposes for which it is intended, including all the purposes for which it is to be advertised or represented, in accord with § 1.106 (b) or (c).

d. If no established name exists for a new-drug substance, the application shall propose a nonproprietary name for use as the established name for the substance.

e. Typewritten or other draft labeling copy may be submitted for preliminary consideration of an application. An application will not ordinarily be approved prior to the submission of the final printed label and labeling of the drug. No application may be approved if the labeling is false or misleading in any particular.

(If the article is a prescription drug, copies of proposed advertising may be submitted optionally for comment or approval.)

7. State whether the drug is (or is not) limited in its labeling and by this application to use under the professional supervision of a practitioner licensed by law to administer it.

8. If this is a supplemental application, full information on each proposed change concerning any statement made in the approved application.

(After an application is approved, a supplemental applica-

tion may purpose changes. A supplemental application may omit statements made in the approved application concerning which no change is proposed. Each supplemental application shall include up-to-date reports of any of the kinds of information required by section 130.13(a) that has not previously been submitted as part of the application, including such submission under the records and reports requirements of section 130.13 or section 130.35. A supplemental application should be submitted for any change beyond the variations provided for in the application (including changes in the scale of production such as from pilot-plant to production batch) that may alter the conditions of use, the labeling, the safety, effectiveness, identity, strength, quality, or purity of the drug or the adequacy of manufacturing methods, facilities or controls to preserve them. Any mailing or promotional piece used after the drug is placed on the market is labeling requiring a supplemental application if it deviates in any significant respect from the approved labeling. When necessary for the safety or effectiveness of the drug, a supplemental application shall specify a period of time within which the proposed change will be made. If a material change is made in the components, composition, manufacturing methods, facilities or

controls, or in the labeling or advertising from the representations in an approved application for a new-drug, and the drug is marketed before a supplement is approved for such change, approval of the application may be suspended or withdrawn as provided in section 505(e) of the act.)

9. It is understood that the labeling and advertising for the new drug will prescribe, recommend, or suggest its use only under the conditions stated in the labeling which is part of this application; and if the article is a prescription drug, it is understood that any labeling which furnishes or purports to furnish information for use or which prescribes, recommends, or suggests a dosage for use of the drug will also contain substantially the same information for its use, including indications, effects, dosages, routes, methods, and frequency and duration of administration, any relevant hazards, contraindications, side effects, and precautions, contained in the labeling which is part of this application. It is understood that all representations in this application apply to the drug produced until an approved supplement to the application provides for a change or the applicant is notified in writing by the Food and Drug Administration that a supplemental application is not required for the change.

Very truly yours,

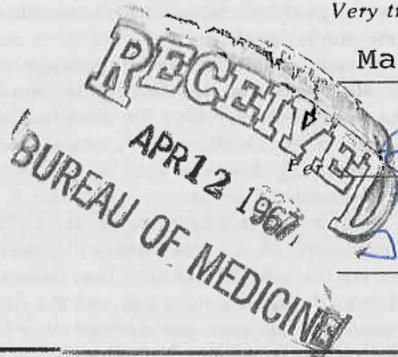
Mallinckrodt Chemical Works

(Applicant)

Almond P. Staley

Technical Director

(Indicate authority)



(1) This application must be signed by the applicant or by an authorized attorney, agent, or official. If the applicant or such authorized representative does not reside or have a place of business within the United States, the application must also furnish the name and post office address of and must be countersigned by an authorized attorney, agent, or official residing or maintaining a place of business within the United States. The data specified under the several numbered headings should be on separate sheets or sets of sheets, suitably identified. The sample of the drug, if sent under separate cover, should be addressed to the attention of the Division of New-Drugs

or the Division of Veterinary Medicine and identified on the outside of the shipping package with the name of the applicant and the name of the drug as shown on the application.

(2) The applicant will be notified of the date on which his application is filed. An incomplete application, or one which has not been submitted in triplicate, will be retained but not filed as an application provided for in section 505(b) of the act. The applicant will be notified in what respect his application is incomplete.

(3) All applications and correspondence should be submitted in triplicate.

**ALL APPLICATIONS AND CORRESPONDENCE SHOULD
BE SUBMITTED IN TRIPPLICATE**

July 6, 1967

Memorandum of Contact

Between: James A. Peterson
Lloyd G. Struttman --- MCW - Mallinckrodt/Nuclear

and Robert W. Jennings --- Bur.Med./Office of New Drugs
Div. of Oncology and Radiopharmaceuticals

Subject: NDA 16-634
Applicant: MCW - M/N
Drug: Cyanocobalamin ⁶⁰Co, Capsules

NDA 16-635
Applicant: MCW - M/N
Drug: Cyanocobalamin ⁵⁷Co, Capsules

On July 6, Mr. Peterson and Mr. Struttman, representatives of Mallinckrodt/Nuclear, visited DOR to discuss pending NDAs. They also talked with Dr. Earl L. Meyers, Dr. Bryant L. Jones, Mr. A. D. Catterson and Mr. M. M. Hein.

I discussed deficiencies (noted as of this time in my reviews) in the manufacturing control information area, for both NDA 16-634 and NDA 16-635.

NDA 16-634/NDA 16-635

The visitors were informed that the letters of March 9, 1967, from (b)(4) authorizing reference to MF (b)(4) in support of the Mallinckrodt/Nuclear NDAs, not provide access to all information associated with the master file. Both Mr. Peterson and Mr. Struttman were aware that the MF included (b)(4) information. They were told MS&D/KL could not authorize reference to (b)(4) material and that an (b)(4) letter of authorization would also be required, before MF (b)(4) could be considered in its entirety in support of the Mallinckrodt NDAs. It was emphasized that at this time only the (b)(4) information in the MF could be reviewed on their behalf.

Mr. Peterson indicated they knew (from (b)(4) of an (b)(4) letter (August 4, 1965) directed toward support of MF (b)(4) and thought this might clear the matter for us. The final paragraph of the referenced letter limits authorization; it does not authorize the divulging of information to (b)(4) or any one else outside of FDA, except in accordance with section 130.32 of the regulations; the paragraph was read to them.

Dr. Meyers also briefed the visitors on the pertinence of section 130.32. We were told additional contacts will be made, in an effort to solve the MF reference problem.

Mr. Peterson was told that part 3 (statement of composition/batch formula, NDA 16-634) did not reflect the approximate amount of cyanocobalamin in the cyanocobalamin Co-60 solution; this will be provided in an amendment.

Mr. Peterson was reminded that stability data would need to be forwarded for review and inclusion in the NDAs. The applications do indicate studies are underway with respect to stability characteristics.

It was pointed out that the applicant should request waiver on the required samples (part 5 of the NDAs), since the drugs are radioactive.

With respect to labels and labeling we commented that labels provided for a "6 month" dating and the package inserts contained radioactive decay charts for 39 weeks (NDA 16-635) and 64 months (NDA 16-634). It was suggested that the charts might encourage a user to employ the drug beyond the expiration date.

Note: Dr. Jones asked that his written report on the conference be included in this memorandum; it follows.


Robert W. Jennings

Medical review memo of conference (Dr. Jones):

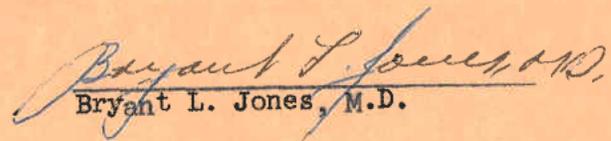
The representatives from Mallinckrodt requested this conference to discuss certain deficiencies in the above two NDA's submissions. The medical review of the summaries were read to Mr. Peterson and to Mr. Struttman and the specific deficiencies in regard to the labeling in these two NDAs were noted. There are four items of importance:

1. Under dosimetry we pointed out a difference in interpretation of a table which influence certain assumptions that would be made in the dosimetry formula. (b) (4)

(b) (4) The company agreed that the dosimetry calculation should be based on the same dose as proposed in the labeling and will amend their submission according to the suggestions made.

2. Also under dosimetry, we pointed out a proofreading error in the marking of the references.
3. Some improper symbols were used in the dosimetry formula.
4. The caption in Table 2 was improper.

The company stated that the editorial corrections would be made and that a submission with new labels would be submitted in the near future. The other items of business were then discussed.'


Bryant L. Jones, M.D.

cc:
Dup NDA
Trip NDA (KAN DO)
M-100
M-160
M-300
M-11
RWJennings/BLJones/smd
7/27/67

MEMORANDUM OF CONFERENCE

NDA: 16-634 and 16-635

July 6, 1967

Between: James A. Peterson, Manager Product Development
Lloyd C. Struttman, Director Med. Isotope Consulting
Mallinckrodt Nuclear
St. Louis, Mo.

AND

Manfred M. Hein, Pharmacologist
Bryant L. Jones, M.D., (part time)
Division of Oncology and Radiopharmaceuticals
Office of New Drugs
Bureau of Medicine

Subject: Cyanocobalamin Co 57 and Cyanocobalamin Co 60 labeled
(NDAs 16-634 and 16-635).

Representatives met at length with Dr. Jones and Dr. Meyers and had conversations with Mr. Jennings. It was only thereafter that they exchanged a few remarks with me. I relayed to them our concern regarding the marketing of Cyanocobalamin with the Co 60 label when the Co 57 label is usually as adequate and offers a lower radiation hazard. It was mentioned that this question has been a problem with a similar product from a different company and that as far as I knew the Co 60 product was never allowed to become an effective NDA. The editorial changes mentioned in the pharmacology review regarding the package insert were called to their attention. Representatives stated that NDA covers the cyanocobalamin capsules only and that they would like to have an opinion as to whether a separate NDA is needed to market the "kit" which also contained intrinsic factor, stable cyanocobalamin, etc. We referred them to Dr. Meyers, as we were not certain on this point.

Mr. Peterson was anxious to have a guideline regarding our needs for pharmacology testing. We stated that this is a matter of product and no firm rules can be made as for instance the data needed for a new agent (i.e. Indium) as a diagnostic agent will be different from that needed for a tagged but otherwise well established agent that is used below therapeutic dosage (Chlormerodin Hg 197 for brain scans). We mentioned that on a new

product used as a radioactive diagnostic agent a survey of the critical and target organs, the turn over rate in these organs, overall metabolism, excretion routes after a single injection, etc. may well be more valuable than conventional extended chronic toxicity studies and will indicate the need for long trials. The submission of a ^{(b) (4)} application seems imminent.

Manfred M. Hein
Manfred M. Hein, Pharmacologist

cc:
~~Orig~~ NDA 16-634 and 16-635
Dup NDA 16-634 and 16-635
Trip NDA 16-634 and 16-635 (SL)
OND
DOR
Med
ODS
BLJones
MMHein/jtm 7/14/67

RJ/DOR



BOX 6172 LAMBERT FIELD • ST. LOUIS, MISSOURI 63145 • 314 AX 1-0540



FORMERLY NUCLEAR CONSULTANTS

RADIOPHARMACEUTICALS

December 11, 1967

NDA 16-635

Division of Oncology and
Radiopharmaceuticals
Office of New Drugs
Bureau of Medicine
Food and Drug Administration
Washington, D.C. 20204

Sincerely yours,

NDA ORIG AMENDMENT

James A. Peterman
Manager, Product Development

Attention Dr. Bryant L. Jones

Gentlemen:

In a telephone conversation on November 30, 1967 with Dr. Bryant Jones, the need for a few minor revisions in the package insert in our pending application covering Cyanocobalamin Co57 Capsules was discussed. The changes have been made in line with the recommendations received.

Enclosed is a complete replacement copy of the package insert for incorporation into the application. The changes being made are briefly as follows: Correction of a typographical error in page 4 under Dosimetry, additions to the Precautions section, incorporating information previously discussed elsewhere in the text, and addition of a new reference to the bibliography.

Questions relating to the stability studies conducted and the expiration date for the product were discussed with Mr. Robert Jennings by telephone on December 5, 1967.

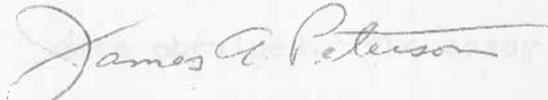
Enclosed is a replacement for Exhibit H, Part 4p, providing additional stability test results on two lots of the product. With the availability of this additional data and the stability information previously submitted, it was agreed that an expiration date of 6 months could be established for the product. This agreement, however, was based on our commitment to continue the stability studies as described in the application, to submit the data as it becomes available, and to withdraw from the market any lots of the product which are found to be unstable within the use period of the product.

Incorporated into the replacement package insert being provided are the changes necessary to provide for this revision in the expiration date. The appropriate change has also been made in the product label and replacement copies of Exhibit H, Part 6, are being provided.

These above revisions in the labeling will appear in the final printed labeling for the product.

Based on the above mentioned telephone conversations and the additional information being provided, we trust that the application can now be viewed as complete.

Sincerely yours,



James A. Peterson
Manager, Product Development

JAP:cd

encl.

RECEIVED
DEC 13 1967
BUREAU OF MEDICINE

	250.	350.	450.	550.
	0.38			0.35
				0.39
		0.51		0.46
			cont.	

... indicate that the capsules exhibit the variation in some of the test results in part, to the relative inaccuracies of the assay procedure.

... the present stability testing program in addition to the lots currently under test, the lots, as they are produced, for continued availability, this data will be forwarded to the manufacturer.

... on the information available and in line with recommendations given in the U.S.P., an expiration date of 6 months from the date of initial standardization of the lot has been established for this product. The product label will bear the following statement: "Do not use after 6 months from the date of manufacturer's standardization."

NDA 16-634
16-635

Mallinckrodt Nuclear
Maryland Heights, Mo. (AF 12-458)

December 5, 1967

MEMORANDUM OF TELEPHONE CONVERSATION

Between: Mr. James A. Peterson - Mallinckrodt

and

Robert W. Jennings, Chemist - BM/DND/DOR

Subject: NDA 16-634 - Cyanocobalamin Co 60
16-635 - Cyanocobalamin Co 57

Mr. Peterson telephoned and referred to their recent conference of November 8, 1967 with this Division (DOR). He inquired into two aspects of previous discussions, namely, receipt of an authorization letter (MF ^{(b)(4)}) and the possibility of using a 6-month expiration dating (with submission of data now available).

Mr. Peterson was informed that today I had located a letter of authorization, directed to the Master-file (i.e. ^{(b)(4)} letter of 8/10/67), which would probably clarify matters with respect to inadequacy based on previous lack of permission to review supporting information. I indicated final conclusions would be reached on the basis of prior review notes and current evaluation. I did express the opinion that at the moment the letter and reference seemed acceptable.

With respect to stability data and revised labeling to show a 6-month, rather than 3-month expiration dating, I acknowledged we had agreed to entertain such a proposal with some 6-month data and a commitment that stability would be followed, submitted when available, and recall instituted if a lot dropped below standard acceptance. The 6-month dating agrees with the U.S.P. for these two articles.

I stated revised labeling should accompany the new amending stability data.


Robert W. Jennings, Chemist

cc:
NDA Dup., Trip.
M-100
M-150
M-14
M-150/RWJennings/smr
1/3/68

MEMORANDUM OF TELEPHONE CONVERSATION

November 30, 1967

Between: Mr. James A. Peterson
Mallinckrodt Nuclear Corp.

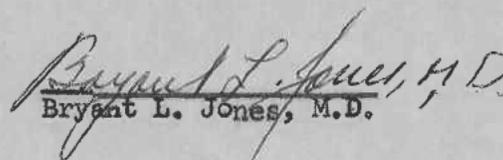
AND

Bryant L. Jones, M.D.
Division of Oncology and Radiopharmaceuticals
Office of New Drugs
Bureau of Medicine

Subject: NDAs 16-634, 16-635 and 16-666

Mr. Peterson was informed that the Medical Review of the revised labeling for these three NDAs had been completed and that some minor corrections and editorial changes were necessary before full approval could be made. These deficiencies and suggestions are covered in detail in the review (Summary) dated November 28, 1967 for NDAs 16-634, 16-635 and 16-666.

Mr. Peterson agreed that the changes were indicated and that he would forward a letter indicating these changes and a statement that the changes would be made as a part of the final printed label.


Bryant L. Jones, M.D.

cc:
Orig NDAs
Dup
Trip
M-100
M-150
M-300
M-14
BLJones/jtm 12/5/67

MEMORANDUM OF CONFERENCE

November 8, 1967

NDA 16-634 Cyanocobalamin Co-60
16-635 Cyanocobalamin Co-57
NDA 16-642 Chlormerodrin Hg-197
(b) (4)
NDA 16-665 Sod. Rose Bengal I-131
16-666 Iodohippurate I-131
NDA 16-698 Sr. Nitrate Sr-85

Between: Mallinckrodt Chemical Works/Mallinckrodt Nuclear
Lloyd G. Struttman
James A. Peterson
Floyd P. Hallett

AND

FDA/BuMed/Division of Oncology and Radiopharmaceuticals
Dr. Earl L. Meyers, Director/DOR
Dr. Bryant L. Jones, M.D.
Dr. David J. Richman, Pharmacologist
Mr. Manfred M. Hein, Pharmacologist
Mr. Charles F. Bruening, Chemist
Mr. Ben Kagan, Chemist
Mr. Alden D. Catterson, Chemist
Mr. Robert W. Jennings, Chemist

Subject: Discussion of current status of the above listed new drug applications, all being radiopharmaceuticals.

NDA's 16/634 and 16-635

The discussion concerning these applications was relatively brief. The applicant had received letters dated October 4, 1967 detailing the incomplete areas found in our reviews of these submissions. Both were incomplete under 505(b)(2),(3),(4) and (6).

We were told amendments were to be submitted to correct deficiencies. The men mentioned that Master File (MF) (b) (4) was to be amended with letters from (b) (4) (b) (4) (the holder of the MF) and (b) (4) (who has supporting information filed in it); they thought the letters may have already been forwarded.

With respect to stability data we understood 3 and 6 month data would be offered now; other data later.

The changes in dosimetry information (package insert), as requested by Dr. Jones, was promised.

NDA 16-642 (b)(4)

(b)(4)

NDA 16-665

Dr. Jones discussed dosimetry problems extant in proposed labeling. He employed his review (summary) notes to detail his objections. The men were told of consistent use of improper symbols, i.e., for example for average beta energy like expression. geometry factor and curie. They were informed (b)(4)

Mr. Hein discussed pharmacology phases. He revealed the submitted animal toxicity data was meager; we were not asking for added animal work at this time (due to available background information); however, additional supporting data on the purified Rose Bengal would be helpful.

The component "purified Rose Bengal" was questioned as a possible new entity, since previously, Rose Bengal has been a mixture not so purified.

Mr. Kagan referred to the terms "certified" and "purified" as found in the application and asked clarification. Mallinckrodt Nuclear is said to receive certified Rose Bengal and purify it.

Dr. Meyers questioned the applicants identification of Rose Bengal. We were told the firm would add their research and development information to the NDA, in support of identity of the article.

The visitors expressed their intention to amend the application with the needed manufacturing and dosimetry information.

During this discussion we were informed the item Rose Bengal I-125 (which appears in the MN catalogue) would probably be dropped.

NDA 16-666

Dr. Jones relayed the results of his review (summary). He detailed dosimetry problems involved (labeling):

- I. Consistent use of improper symbols
 - a) average energy expression;
 - b) geometry factor;
 - c) curie
- II. Calculations
 - a) [redacted] (b)(4)
- III. Reference
 - a) [redacted] (b)(4)
 - b) [redacted]
 - c) etc. other values

Dr. Richman discussed pharmacology aspects with respect to labeling:

- a) "Contraindicated in women of child bearing capacity and during lactation" should be included, rather than present statement; of course with exception where physician decides otherwise with full knowledge of warning.
- b) Precaution section --- renal function.

Mr. Kagan indicated the application, as it pertained to manufacturing controls, was passable.

The Mallinckrodt Nuclear representatives stated the NDA would be amended to provide revised labeling, a request for waiver for samples and an expiration date.

NDA 16-698

Because of limited review this application was discussed only briefly. The gentlemen were told manufacturing information from the basic supplier would probably be needed and dosimetry information revisions would probably be required.

cc: Robert W. Jennings, Chemist
 Orig NDAs 16-634/635 16-642/ (b)(4) 16-665/666 16-698
 Dup Trip (SL) M-100 M-150 M-300 M-14
 ELMeyers BLJones DJRichman MMHein CFBruening BKagan ADCatterson
 RWJennings/jtm 12/4/67

Dr # 5

PERSONALLY SUBMITTED BY ✓

RESUBMISSION
NDA ORIG AMENDMENT



BOX 6172 LAMBERT FIELD, ST. LOUIS, MISSOURI 63145 • 314 AX 1-08



FORMERLY NUCLEAR CONSULTANTS

RADIOPHARMACEUTICALS

November 7, 1967

NDA 16-635

Earl Meyers, Ph.D.
Director, Division of Oncology
and Radiopharmaceuticals
Office of New Drugs
Bureau of Medicine
Food and Drug Administration
Washington, D.C. 20204

Dear Dr. Meyers:

In response to the letter of October 4, 1967 from Dr. Robert M. Hodges and our earlier discussions with you and Dr. Bryant Jones, we are providing additional information to be included in NDA 16-635. The following summarizes the information being provided.

1. Addition to Part Iaiii, p. 2, describing two cases of questionable clinical results with the product.
2. Replacement for p. 5, Part 2, providing an expanded description of the hard gelatin capsules used for the product. Included, as a new Exhibit A, Part 2, is information from (b) (4) on the quantitative composition of the capsules.
3. Replacement for p. 10, Part 4i, to more adequately describe the capsules used in preparing the product.
4. Replacement for p. 11, Part 4o. The lot mark example was changed to show the currently employed system in which the product code number is part of the lot mark.
5. Replacement for Exhibits A and B, Part 4d. In Exhibit A the radiochemical purity test is included as part of the routine testing. Since the pH of the solution is adjusted during the processing of the capsules, we do not consider the pH of the raw material to be critical. The notation relating to this pH test was changed as follows: "The following U.S.P. test is normally not conducted." For Exhibit B the wording of the notation applying to the U.S.P. tests not considered applicable has also been changed as above.

6. Replacement for Exhibit C, Part 4d. It has come to our attention that the specifications and test methods sheet for (b)(4) was inadvertently provided initially rather than the proper one for (b)(4). This correction is being made with the replacement pages for Exhibit C.
7. Replacement for Exhibit G, Part 4d. In the first U.S.P. XVII supplement, the limits for radioactivity assay were changed from (b)(4) % of the labeled value to (b)(4) %. This change has been made in our specifications as shown in the new Exhibit G.
8. An addition to Part 4p and a new Exhibit H, Part 4P, are included providing a description and the results of the stability studies conducted on the drug. As is pointed out, a 3 month expiration is being proposed pending the availability of additional data to support the 6 month use period suggested by the U.S.P.
9. Replacement for p. 13, Part 5. A waiver of the sample requirements is requested in Part 5ai. Included as a new Exhibit C, Part 5aiii, is a copy of a gamma spectrum obtained with a 512 channel pulse height analyzer.
10. Replacement for Exhibit A, Part 6. The expiration statement on the label is changed to read: (b)(4)
11. Replacement for Exhibit B, Part 6. A complete replacement for the package insert is being provided rather than the specific pages on which appropriate changes have been made. The following revisions have been incorporated in this replacement for Exhibit B.
 - a) p. 1. Change in the expiration date.
 - b) p. 2. Correct ^{57}Fe to ^{57}Co in second paragraph under Physical Characteristics; change reference 22 to 21, and change reference 21 to 20, and revise accompanying statement.
 - c) p. 3 & 4. Suggested changes made in the Dosimetry section.
 - d) p. 5. Include strongly recommended under Precautions.

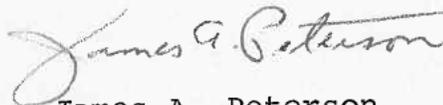
- e) p. 10. Under How Supplied, all references to products other than Cyanocobalamin Co57 Capsules are deleted and the statement covering the expiration date is revised. As suggested, the time shown on the decay table is reduced to 90 days (3 months), the recommended use period of the product.
- f) p. 12. Reference No. 20, Smith, E. M., Properties, Uses, Radiochemical Purity and Calibration of Tc^{99m}, J. Nucl. Med., 5:871-882, 1964, has been deleted since it was not applicable.

With regard to the question of our reference to Master File MF (b)(4), we have discussed this matter with representatives of (b)(4). They in turn discussed the subject with (b)(4). We have been advised by (b)(4) that the authorization necessary to complete our reference to MF (b)(4) has been supplied to the FDA. With this authorization we hope that MF (b)(4) will be fully available to support this application.

As provided in regulations, we request a waiver of the summary requirement for this application.

To the best of our knowledge, all of the points which have been raised concerning the completeness of this application have been clarified or revised in accord with recommendations received. We trust that the application may now be considered complete and approvable.

Sincerely yours,



James A. Peterson
Manager, Product Development

JAP:cd

encl.

RECEIVED

NOV - 8 1967

BUREAU OF MEDICINE

NDA 16-635

AF: 12-458

OCT 4 1967

Mallinckrodt Chemical Works (Mallinckrodt/Nuclear)
Attention: Floyd P. Hallett
2703 Wagner Place
Maryland Heights, Missouri 63042

Gentlemen:

Reference is made to your new drug application dated April 7, 1967 submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for the preparation Cyanocobalamin Co 57 Capsules.

The application is incomplete under sections 505(b)(2) and (3) of the Act as follows:

It fails to contain a full statement of the components and quantitative composition of the drug. In particular, the application does not contain a statement of the components and quantitative composition for the capsule employed, to include any colors used.

Further, "Exhibit G, Part 4d" and page "10" of the application do not agree with respect to capsule information.

The application is incomplete under section 505(b)(4) of the Act as follows:

It fails to contain a full description of the methods used in and the facilities and controls used for the manufacture, processing and packing of the drug. We are unable to fully consider the Master File, MF ^{(b)(4)}, in support of the application, as discussed with your representatives, James A. Peterson and Lloyd G. Struttman, on July 6, 1967.

Additionally, it fails to include a complete description of and the data derived from, studies of the stability of the drug.

Information in the application concerning the components Cyanocobalamin Co 57 Solution USP and Cyanocobalamin Injection USP (Exhibits A and B, Part 4d) refers to various USP tests that will be run only when requested. We ask that you provide an amending explanatory statement as to when these might be regarded as necessary.

As discussed in person on July 6, 1967 between your representatives, Mr. J. A. Peterson and Mr. L. G. Struttman, and Dr. Bryant L. Jones of this Administration, the application is regarded as incomplete under section 505(b)(6) of the Act. Our objections to labeling were reviewed in detail at the conference and we understand revised labeling will be forwarded. Briefly, several aspects of dosimetry information, as proposed by the package insert, were discussed.

On the basis of review by our pharmacologists we find this application approvable at this time if certain minor changes are made in the package insert.

1. There is a typographical error under physical characteristics in that ^{57}Fe instead of Co^{57} is referred to in your current proposal.
2. The use of a flushing nose under "Precautions" should be strongly recommended.
3. The references to standardization in the brochure and label should indicate factory standardization, since the user may standardize the product himself and use it for 6 months thereafter.
4. The decay table should be limited to 6 months duration, so it will not invite use beyond that time.

Since the application is incomplete under section 505(b)(2), (3), (4) and (6) of the Act, it may not be filed as an application provided for in section 505(b).

Sincerely yours,

RMH 10.3.67

Robert M. Hodges, M.D.
Director, Office of New Drugs
Bureau of Medicine

cc:

- ~~Orig NDA~~
- Dup
- Trip (SL)
- M-100
- M-160
- M-300
- M-14
- M-12
- M-1

R/D Endorsed by: RWJennings 8/21/67; CFBruening 8/22/67; BLJones 8/23/67;
DJRichman 9/7/67 *off 9/5*

RWJennings (M-160)/jtm 9/15/67

RJ 9/15

E L Meyers 9/18/67

BS Jones 9/15/67

CF Bruening 9.15.67

NDA 16-635

AF: 12-458

FEB 19 1968

Mallinckrodt Chemical Works (Mallinckrodt/Nuclear)
Attention: Floyd P. Hallett
2703 Wagner Place
Maryland Heights, Missouri 63042

Gentlemen:

Reference is made to your new drug application dated April 7, 1967 submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for the preparation Cyanocobalamin Co 57 Capsules.

We also acknowledge receipt of your additional communications dated November 7, 1967, December 11, 1967 and January 4, 1968 amending the application.

We have completed the review of this application as submitted with draft labeling. However, before the application may be approved, it will be necessary for you to submit final printed labeling. The labeling should be identical in content to the draft copy. If additional information relating to the safety or effectiveness of this drug becomes available before we receive the final printed labeling, revision of that labeling may be required.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

Please submit twelve copies of the printed labels and other labeling.

Sincerely yours,

cc:

~~Orig NDA~~
Dup
Trip (KAN DO)
M-1
M-100
M-150
M-300
M-14
M-12

Herbert L. Ley, Jr., M.D.
Director
Bureau of Medicine

B.D. Drincher
2/15/68

R/D Endorsed by: RMHodges; CFBruening 1/31/68
BLJones 1/31/68
CFBruening/jtm 2/12/68

E.L. Meyer 2/12/68
m.m. Wein 2/12/68
hwp 2/14/68

CFBruening
2/12/68

Herbert L. Ley, Jr., M.D.
Director, Bureau of Medicine

February 12, 1968

Director, Office of New Drugs

NDA 16-635 - Cyanocobalamin Co 57 Capsules
Mallinckrodt Chemical Works

This product is used for the same indications as the Cobalt 60 application (NDA 16-634) of this firm which was approved by you this week. Because of the shorter half-life it is probably the preferred cobalt isotope. The labeling is the same as the Cobalt 60 except for the different isotope.

Approval of this application is recommended.

Robert M. Hodges, M.D.

cc:

Orig NDA

Dup NDA

Trip NDA (KAN-DO)

M-100

M-150

M-300

M-14

RMHodges:pas

MEMO RECORD	AVOID ERRORS PUT IT IN WRITING	DATE
FROM: R Ellenberg		OFFICE
TO: Dr. Manshew B.M. 2/15/68		DIVISION
SUBJECT: 16-635 Cyanocobalamin CO 57 Capsules		
<p>SUMMARY</p> <p>This is an original approved letter. The labeling is almost identical to that for Cyanocobalamin CO 60. Both drugs are USP and both have an expiration date of 6 months. The half life of CO 60 is 5.27 years while that of CO 57 is 270 days. This means that at the end of six months the radioactivity of CO 57 is only $\frac{2}{3}$ of that when it was standardized. However, since the date of standardization is given on the drug container the physician can calculate radioactivity.</p> <p>Stability data has been submitted solely on the basis of the Cyanocobalamin since the rate of decay is well established.</p> <p>The medical summary points out certain changes that need to be made. As far as I can determine all of these have been accomplished.</p> <p style="text-align: right;">R Ellenberg 2/14/68</p> <p>To Mr. Key - for sign.</p> <p style="text-align: center;">B.J. Minchew 2/15/68</p> <p style="text-align: center;">Signed 2/19/68 T. Key</p>		
SIGNATURE	DOCUMENT NUMBER	

MEMORANDUM OF TELEPHONE CONVERSATION

NDA: 16-634 and 16-635

January 31, 1968

Between: James A. Peterson
Mallinckrodt Chemical Works (Mallinckrodt/Nuclear)
Maryland Heights, Missouri

AND

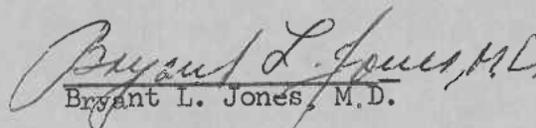
Bryant L. Jones, M.D.
Division of Oncology and Radiopharmaceuticals
Office of New Drugs
Bureau of Medicine

The applicant was contacted this date regarding NDA 16-634 and NDA 16-635 to call attention to two minor errors in the proposed package insert labeling.

On page 5, line 6 of the last paragraph, the word "adsorption" should be "absorption."

On page 7, line 3 from the bottom, the word "of" should be inserted between "presence intrinsic."

With the agreement of the company representative, these pen and ink corrections were made.


Bryant L. Jones, M.D.

cc:

~~Orig NDA~~

Dup

Trip (KAN DO)

M-100

M-150

M-300

M-14

BLJones/jtm 1/31/68

Mr. Charles F. Bruening, Supervisory Chemist
Division of Oncology and Radiopharmaceuticals

January 18, 1968

Robert W. Jennings, Chemist
Division of Oncology and Radiopharmaceuticals

Mallinckrodt/Nuclear
Maryland Heights, Mo.

EIR August 16-23, 1967

NDA 16-634
NDA 16-635

NDA 16-634 ---- Cyanocobalamin Co-60
NDA 16-635 ---- Cyanocobalamin Co-57

Mallinckrodt/Nuclear was inspected only five (5) months ago,
August 16-23, 1967, with respect to these NDAs ---- among others.

The firm was reported as expanded, with the expectation of additional
construction in September.

An error in information submitted to the NDA, with respect to
the component (b) (4) vs. (b) (4) was
noted. The NDAs have been corrected and the inspector found no
error in use of a wrong compound.

There was an error in dispensing 4 capsules of Cyanocobalamin
Co-57 to (b) (4) --- The capsules were
labeled 0.7 microgram of cyanocobalamin per capsule, rather than
0.32 microgram. Other dispensing from the lot showed proper
labeling. Possible typing error --- did not result in a com-
plaint. No significant complaints were found in the complaint
file on either NDA drug.

The firm has promised correction of control weaknesses.

cc:

~~Orig NDAs~~

Dup

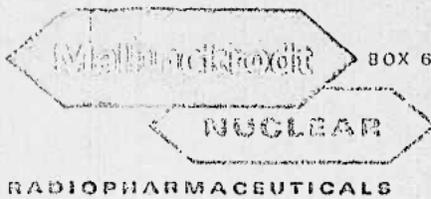
Trip

M-100

M-150

RWJennings/jta 1/18/68

NEW CORRES ✓
J. Collins
1/11/68



BOX 6172 LAMBERT FIELD • ST. LOUIS, MISSOURI 63145 • 314 AX 1-0540

RADIOPHARMACEUTICALS

January 4, 1968

Orig

Division of Oncology and
Radiopharmaceuticals
Office of New Drugs
Bureau of Medicine
Food and Drug Administration
Washington, D.C. 20204

RECEIVED Orig

JAN 12 1968

Attention Dr. Bryant L. Jones

DIR/DOH
BUREAU OF MEDICINE
FOOD AND DRUG ADMINISTRATION, DHEW

Gentlemen:

This is to confirm our telephone conversation with Dr. Bryant L. Jones on January 3, 1968. Based on recommendations received from Dr. Jones, we agree to revise the format of the package inserts presently included in all of our pending New Drug Applications. Included in this group are NDAs No. 16-634, 16-635, 16-642, ^{(b)(4)}, 16-665, 16-666, 16-698 and 16-708.

When final printed labeling is prepared, the various sections of the package insert will be rearranged into the following preferred sequence. The content, however, will be identical to that presently provided in the applications.

- | | |
|----------------------|----------------------------|
| 1. Introduction | 7. Precautions |
| 2. Identification | 8. Adverse Reactions |
| 3. Pharmacology | 9. Dosage & Administration |
| 4. Indications | 10. Clinical Studies |
| 5. Contraindications | 11. How Supplied |
| 6. Warnings | 12. References |

The package insert included in any new applications will be arranged in this format at the time of initial submission.

Sincerely yours,

James A. Peterson

James A. Peterson
Manager, Product Development

RECEIVED 1 COPY
STATS OF
MATERIAL MADE
DATE _____
JAP/ba

RECEIVED

JAN 5 - 1968

BUREAU OF MEDICINE

Mallinckrodt

BOX 10172 LAMBERT FIELD • ST. LOUIS, MISSOURI 63145 • 314 AX 1.0540

NUCLEAR

ORIGINAL FPL
Blalock 5/3/68

April 29, 1968

Ref. Cyanocobalamin Co57 Capsules
NDA 16-635

Department of Health, Education
and Welfare
Food and Drug Administration
Washington, D.C. 20204

Gentlemen:

This is in response to your letter dated February 19, 1968 indicating that the above NDA may be approved subject to review of the final printed labeling for the drug. As requested, we are enclosing 12 copies each of the product label and package insert.

The format for the package insert has been arranged in the manner requested by Dr. Bryant L. Jones and confirmed in my letter dated January 4, 1968. In addition, a typographical error in the formula for the calculation of the percent of Cyanocobalamin Co57 excreted in the urine (step 8, p. 6) has been corrected. This correction provides for a multiplication factor of 500 in the equation, to correct for the use of a 4 ml aliquot taken from the total 2000 ml patient urine sample (steps 5 and 7, p. 6) when performing the test. Also, the Radioactive Decay table, immediately preceding the list of Selected References, has been extended to 180 days (6 months) to provide for the entire use life of the product. With these two corrections, the labeling is identical in content to the draft copy previously submitted.

We trust that with the submission of this final labeling it will be possible to obtain approval of this application.

Sincerely yours,

James A. Peterson

James A. Peterson
Assistant Director
Biomedical Research

RECEIVED

MAY 7 1968

OND/OOR
BUREAU OF MEDICINE

FOOD AND DRUG ADMINISTRATION, DREW



JAP:cd

encl.