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Paul C. Aebersold, Director, Isotopes Division June 23, 1954

Kenneth Kasschau, Director, Research and Medicine Division

RADIOISOTOPES FOR DRUG APPLICATIONS

SYMBOL: ORB:CSS

The enclosed letter from ORNL under date of June 17, 1954, together with processing information on Iodine and Phosphorus, is in reply to my letter of June 1, subject as above. The radioisotopes processing information is included in response to Item 2, page 2 of my letter to the Laboratory.

In the letter from the ORNL we are asked to supply a text for statements to be included in shipments. We will appreciate your comments and recommendations regarding labelling and information to be supplied in conformation with Food and Drug Administration requirements.

Kenneth Kasschau

Enclosure:
Ltr CEL to KK dtd 6/17/54.

CC: N. H. Woodruff
J. Wallace Ould, Jr.

Shoup:ef

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FOLDER Chief Counsel 19 of 49 HRE 67

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AUG 5 1954

1184442

ISOTOPES PROGRAM - 5

STANDARD FORM NO. 54

Office Memorandum • UNITED STATES GOVERNMENT

TO : J. Wallace Ould, Jr., Assistant General Counsel

DATE: June 23, 1954

FROM : Kenneth Kasschau, Director, Research and Medicine Division

SUBJECT: RADIOISOTOPES FOR DRUG APPLICATIONS

SYMBOL: ORB:CSS

Enclosed is a copy of my letter to ORNL on June 1, 1954, subject as above, with reference to modification of labelling and the supplying of information in conformance with Food and Drug Administration requests and regulations. The enclosed reply from the Laboratory on June 17, calls for our supplying a text for Iodine and Phosphorus labelling.

Copies of the enclosed letters with I^{131} and P^{32} processing information as requested under item 2, page 2 of my letter to the Laboratory, are also being forwarded to the Isotopes Division for inclusion with their material prepared for Commissioner Harvey.

We will appreciate your review and comments, and your suggestions regarding legal precautions in the wording of labels or statements supplied with shipments.

Herman McKelly

Kenneth Kasschau

Enclosures:
1. Ltr CEL to KK dtd 6/17/54.
2. Ltr KK to CEL dtd 6/1/54.

CC: N. H. Woodruff
P. C. Aebersold

Sheup:ef

On same to Carbide letter prepared by R&M, and coordinated with Iso Div. and AGC. No further reply to this memorandum will be necessary.

1184443

ISOTOPES PROGRAM - 3

505

OAK RIDGE NATIONAL LABORATORY
OPERATED BY
CARBIDE AND CARBON CHEMICALS COMPANY
A DIVISION OF UNION CARBIDE AND CARBON CORPORATION

UCC

POST OFFICE BOX P
OAK RIDGE, TENN

June 17, 1954

U. S. Atomic Energy Commission
Post Office Box E
Oak Ridge, Tennessee

Attention: Mr. Kenneth Kasschau

Subject: RADIOISOTOPES FOR DRUG APPLICATIONS

Gentlemen:

In accordance with your letter of June 8, on the above subject, we are making arrangements to add the words "pharmaceutically unrefined" to the bottle labels we use for I^{131} and P^{32} shipments. It will be necessary to have a new supply printed for this purpose. As soon as the proper text is received from your office, we will also prepare a small printed card or booklet to be included with each I^{131} and P^{32} shipment.

Attached are copies of our methods for producing and analyzing I^{131} and P^{32}.

Concerning the purity of our I^{131} and P^{32} preparations, we have heard of no cases, since we started shipments in 1946, where ill effects were suffered by persons to whom our I^{131} and P^{32} preparations were administered which could be attributed to chemical impurities, mistaken identity, or gross inaccuracies in our assays. Although it is the policy of the AEC that ORNL can make no guarantee of the sterility, purity, or strength of radioisotope preparations, we have always striven to produce material of the highest purity.

If more information is required, it is suggested that a visit of Food and Drug Administration personnel to the Laboratory for personal conversations and inspection would be the best way to work out any remaining details.

Very truly yours,

CEL:AFR:jml

OAK RIDGE NATIONAL LABORATORY

cc: C. E. Center
A. F. Rupp
E. J. Witkowski

C. E. Larson

C. E. Larson
Director

Encl. #1 1184444

SUMMARY OF THE I^{131} PROCESS

Radioiodine is formed by the fission of uranium in the ORNL graphite reactor. No carrier is added to the product; the only inactive iodine present is that formed as a result of fission or from traces of impurities in the reagents. To keep the accumulation of inactive iodine to a minimum, pure reagent-grade chemicals and slugs with less than 100 days' bombardment time are used.

The aluminum jackets are removed from the slugs, and the uranium is washed with several water washes and 10% nitric acid solution at 80°C, to make sure that all traces of the coating-removal solution are removed prior to dissolution of the uranium metal. The uranium metal is then dissolved in nitric acid.

To remove the I^{131} from the uranyl nitrate solution, air and steam are bubbled through at the boiling point (about 114°C) and the iodine is distilled out. Several factors determine how much of the iodine is removed, most important of which are those conditions that affect the valence state of the iodine. Iodine vapor, along with some nitric acid and nitrogen oxide vapors, is passed to a condenser and caught in the condensate.

The 24 liters of acid condensate containing radioiodine usually obtained per run is split into two 12-liter batches and processed separately. It should be pointed out that the dividing of processing solutions is not a processing requirement, but is necessary because the old equipment must be operated beyond design capacity; in the new I^{131} plant, division of process solutions will not be necessary. Each batch is slowly drained to a stainless steel still which contains previously prepared 6 liters of 17% hydrogen peroxide chilled to 10-15°C. The resulting mixture is allowed to react for 20 minutes to oxidize the nitrous acid to nitric acid. The solution is then heated to boiling by means of a steam coil, and iodine is distilled into a solution of 60 grams of sodium hydroxide in 12 liters of water. Small amounts of nitric acid come over during distillation. The alkaline solution converts the elemental iodine to a mixture of sodium iodide and sodium iodate, which is then reduced in volume by boiling in a steam-heated stainless steel evaporator and held in the evaporator until the second portion of the run is added to it.

During the above-described processes, a negative pressure is kept on the equipment to prevent leakage of gaseous iodine. Before discharging the air taken from the equipment, it is passed through a sodium hydroxide scrubber containing 14 liters of 8 N sodium hydroxide solution. During the course of a run, NO_2 is passed through the scrubber, neutralizing a large portion of the caustic until the final volume is about 20 liters and approximately 2 N basic. In addition to neutralizing the NO_2, approximately 500-1000 mc of I^{131} is also scrubbed out of the acid vapors. The scrubber solution is also processed to recover I^{131}.

All the above processing is done in fairly large, stainless steel equipment, remotely operated. The final purification is done in small Pyrex glassware which is also operated remotely.

The concentrated alkaline solution containing iodine is transferred to a Pyrex glass flask and 1 N potassium permanganate is added to oxidize any reducing materials present and take the iodine to iodate. Sulphuric acid is added carefully, first to neutralize the caustic present and then to bring the H_2SO_4 content up to 20%. The solution is heated to distill off HNO_3 or other volatile impurities while a 10% reduction in volume is being made; iodine remains in the flask as non-volatile

1184445

iodate. Phosphorous acid is added to the flask to reduce the excess permanganate, indicated by removal of the pink color, and reduce iodate to elemental iodine. The distillation is resumed and five 100-ml portions of distillate are collected, each distilled into a solution made up of 6 ml of 0.38 N sodium hydroxide and 4 ml of 0.1 M sodium sulphite. The sodium sulphite is used to ensure the reduction of iodine to iodide and prevent accidental volatilization of iodine if the product should be made acidic.

The combined distillate is evaporated to about 450 ml volume, passed thru a fine sintered glass filter, and put into a Duraglas bottle for storage. Samples are taken and analyzed for the following:

(1) Non-Iodine activity (identification), and radiochemical purity

(2) I^{131} and I^{133} assay.

(3) Heavy metals

(4) Total solids

(5) Nitrates.

The tests used for analysis of the products are as follows:

(1) Non-iodine activity (identification and purity) is determined by the conversion of the iodine in a sample to free iodine and heating to volatilize the iodine; the residue is counted with an end window Geiger-Mueller counter to determine whether or not any activity (non-iodine activity) remains.

(2) I^{131} and I^{133} activities are measured by using a high pressure gamma ionization chamber and a NaI crystal scintillation counter. Both instruments are calibrated with I^{131} standards that have been counted with a π counter. The percentage of I^{133} in the sample is calculated from the uranium irradiation time and the decay time.

(3) Heavy metals are determined quantitatively by use of the sulfide precipitation test, using lead as a standard.

(4) Total solids are determined as that material which does not evaporate or ignite at a temperature of 100°C for one hour.

(5) The nitrate content is estimated by the Brown Ring Test.

In addition to these routine tests, periodic complete radiochemical analyses are made for check purposes.

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I^{131} products meet the following specifications.

Chemical Form:	NaI in basic Na_2SO_3 solution
Radiochemical Purity:	> 99% (test limit)
Concentration:	5-20 mc/ml
Total Solids:	< 2 mg/mc*
Specific Activity:	Carrier-free**
Basicity:	0.005 N to 0.05 N (NaOH)
Heavy Metals:	< 10 ppm

* The solids are from the added NaOH and Na_2SO_3.

** We use the term "carrier-free" to mean "No added carrier."

AFR:PBO:jml

June 16, 1954

1184447

PROCEDURE FOR MANUFACTURE OF PHOSPHORUS 32

Radiophosphorus (P^{32}) is formed by the n-p reaction of fast neutrons on elemental sulfur. Special cans containing 2500 grams of sulfur are bombarded for approximately seven weeks in the ORNL graphite reactor. The can used to contain the sulfur is made of high-purity aluminum and after a period of decay it can be reused, for only a small amount of short-lived radioactivity is induced in the metal.

The irradiated sulfur is removed from the can by melting it out into a Pyrex glass tube inside a vertical autoclave. One liter of 0.2 N nitric acid is poured on top of the sulfur. The glass tube is covered with a Teflon plastic lid, and a small amount of water is poured around the outside of the tube, between the tube and autoclave wall. The autoclave is closed and steam at 45-pound pressure is applied to the autoclave jacket, heating to a temperature of 135°C, which melts the sulfur in the tube. By leaving the molten sulfur in contact with the 0.2 N nitric acid for about ten hours, approximately 60% of the phosphorus is extracted out of the molten sulfur into the nitric acid solution.

After the sulfur is extracted, it is cooled and the 0.2 N nitric acid containing the $P^{32}O_4$ ions is transferred by means of vacuum to glassware equipment for purification. At this point, the solution contains silica, iron, chromium, nickel, nitrates, sulfates and traces of many other elements extracted from the sulfur.

The extract solution is boiled to near dryness to reduce volume and remove volatile acids. The $P^{32}O_4$ remains in the evaporator flask and is taken up in a known volume of 0.05 N nitric acid. This solution is passed through a cation resin bed (Dowex-50) and the bulk of the cations exchanged for H^+, the $P^{32}O_4$ going through the resin bed into the effluent. Three hundred fifty milligrams of lanthanum as the nitrate is added to the effluent from the ion exchange bed and enough ammonium hydroxide is added to make the solution slightly basic, precipitating the lanthanum as the hydroxide. This precipitation step co-precipitates the $P^{32}O_4$ as lanthanum phosphate almost quantitatively. The filtrate from the precipitation, containing all the other anions which were originally present, is discarded. The lanthanum hydroxide precipitate is washed with water adjusted to pH 7 and these washes are also discarded. The precipitate is then dissolved in 0.05 N nitric acid and passed through another cation resin (Dowex 50) bed to remove the lanthanum.

At this point in the process, inactive phosphorus (P^{31}) is added to the P^{32} in the amount of 0.00025 gram of P^{31} per mc of P^{32}.

The P^{32} is now essentially pure, but to make sure that no organic matter has come through the process, the effluent from the second cation bed containing the P^{32} is boiled just to dryness and treated with 70% nitric acid and 30% hydrogen peroxide. This solution is evaporated carefully to incipient dryness, then dissolved in 0.05 N nitric acid and passed through a third cation resin bed to make sure that only H^+ cations remain. The effluent from the resin bed contains the P^{32}, which is taken to dryness to remove the HNO_3, and the product is dissolved in approximately 450 ml of 0.025 N hydrochloric acid. This is the product solution which is analyzed for the following.

1184448

(1) P^{32} activity, identification by absorption study, radiochemical purity

(2) Total solids

(3) Non-volatile material

(4) Acidity

(5) Heavy metals

(6) Test for precipitation at pH 7

The tests used for the analysis of the P^{32} products are as follows.

(1) P^{32} activity is determined by the evaporation of the aqueous sample, which leaves the radioactive P^{32} in a dry form on a very thin polystyrene backing material, and subsequent counting of the emitted beta particles by means of an end window Geiger-Mueller counter. Periodic checks are made, using Bureau of Standards P^{32} standards. Absorption curves and decay studies are made to establish identity and radiochemical purity.

(2) Total solids are determined as that material which does not evaporate or ignite when held at a temperature of 100°C for one hour.

(3) Non-volatile materials are determined as that material which does not evaporate or ignite at a temperature of 600°C for one hour.

(4) Acidity is determined by titration of an aliquot against a standard basic solution.

(5) Heavy metals are determined by the sulfide precipitation (colorimetric) test against a lead standard.

(6) The precipitation test is made by adding silica-free sodium hydroxide to an aliquot of the product, adjusting to pH 7-8. The sample is heated at 70°C for four hours. A comparison is made with a standard in a Tyndallometer to determine the degree of precipitation.

P^{32} products meet the following specifications.

Chemical Form:	Phosphate in weak HCl
Radiochemical Purity:	$>99\%$ (test limit)
Concentration:	>0.5 mc/ml
Total Solids:	<5 mg/mc
Specific Activity:	$\sim 40,000$ mc/g P
Precipitate at pH 7-9:	Nil

AFR:PBO:jml
June 16, 1954

1184449

PROCEDURE FOR MANUFACTURE OF PHOSPHORUS 32

Radiophosphorus (P^{32}) is formed by the n-p reaction of fast neutrons on elemental sulfur. Special cans containing 2500 grams of sulfur are bombarded for approximately seven weeks in the ORNL graphite reactor. The can used to contain the sulfur is made of high-purity aluminum and after a period of decay it can be reused, for only a small amount of short-lived radioactivity is induced in the metal.

The irradiated sulfur is removed from the can by melting it out into a Pyrex glass tube inside a vertical autoclave. One liter of 0.2 N nitric acid is poured on top of the sulfur. The glass tube is covered with a Teflon plastic lid, and a small amount of water is poured around the outside of the tube, between the tube and autoclave wall. The autoclave is closed and steam at 45-pound pressure is applied to the autoclave jacket, heating to a temperature of 135°C, which melts the sulfur in the tube. By leaving the molten sulfur in contact with the 0.2 N nitric acid for about ten hours, approximately 60% of the phosphorus is extracted out of the molten sulfur into the nitric acid solution.

After the sulfur is extracted, it is cooled and the 0.2 N nitric acid containing the $P^{32}O_4$ ions is transferred by means of vacuum to glassware equipment for purification. At this point, the solution contains silica, iron, chromium, nickel, nitrates, sulfates and traces of many other elements extracted from the sulfur.

The extract solution is boiled to near dryness to reduce volume and remove volatile acids. The $P^{32}O_4$ remains in the evaporator flask and is taken up in a known volume of 0.05 N nitric acid. This solution is passed through a cation resin bed (Dowex-50) and the bulk of the cations exchanged for H^+, the $P^{32}O_4$ going through the resin bed into the effluent. Three hundred fifty milligrams of lanthanum as the nitrate is added to the effluent from the ion exchange bed and enough ammonium hydroxide is added to make the solution slightly basic, precipitating the lanthanum as the hydroxide. This precipitation step co-precipitates the $P^{32}O_4$ as lanthanum phosphate almost quantitatively. The filtrate from the precipitation, containing all the other anions which were originally present, is discarded. The lanthanum hydroxide precipitate is washed with water adjusted to pH 7 and these washes are also discarded. The precipitate is then dissolved in 0.05 N nitric acid and passed through another cation resin (Dowex 50) bed to remove the lanthanum.

At this point in the process, inactive phosphorus (P^{31}) is added to the P^{32} in the amount of 0.00025 gram of P^{31} per mc of P^{32}.

The P^{32} is now essentially pure, but to make sure that no organic matter has come through the process, the effluent from the second cation bed containing the P^{32} is boiled just to dryness and treated with 70% nitric acid and 30% hydrogen peroxide. This solution is evaporated carefully to incipient dryness, then dissolved in 0.05 N nitric acid and passed through a third cation resin bed to make sure that only H^+ cations remain. The effluent from the resin bed contains the P^{32}, which is taken to dryness to remove the HNO_3, and the product is dissolved in approximately 450 ml of 0.025 N hydrochloric acid. This is the product solution which is analyzed for the following.

1184450

(1) P^{32} activity, identification by absorption study, radiochemical purity

(2) Total solids

(3) Non-volatile material

(4) Acidity

(5) Heavy metals

(6) Test for precipitation at pH 7

The tests used for the analysis of the P^{32} products are as follows.

(1) P^{32} activity is determined by the evaporation of the aqueous sample, which leaves the radioactive P^{32} in a dry form on a very thin polystyrene backing material, and subsequent counting of the emitted beta particles by means of an end window Geiger-Mueller counter. Periodic checks are made, using Bureau of Standards P^{32} standards. Absorption curves and decay studies are made to establish identity and radiochemical purity.

(2) Total solids are determined as that material which does not evaporate or ignite when held at a temperature of 100°C for one hour.

(3) Non-volatile materials are determined as that material which does not evaporate or ignite at a temperature of 600°C for one hour.

(4) Acidity is determined by titration of an aliquot against a standard basic solution.

(5) Heavy metals are determined by the sulfide precipitation (colorimetric) test against a lead standard.

(6) The precipitation test is made by adding silica-free sodium hydroxide to an aliquot of the product, adjusting to pH 7-8. The sample is heated at 70°C for four hours. A comparison is made with a standard in a Tyndallometer to determine the degree of precipitation.

P^{32} products meet the following specifications.

Chemical Form:	Phosphate in weak HCl
Radiochemical Purity:	$>99\%$ (test limit)
Concentration:	>0.5 mc/ml
Total Solids:	<5 mg/mc
Specific Activity:	$\sim 40,000$ mc/g P
Precipitate at pH 7-9:	Nil

AFR:PBO:jml
June 16, 1954

1184451

T. A. Jones, Chemistry Branch, Division of Research, Washington

June 18, 1954

Paul C. Aebersold, Director, Isotopes Division, Oak Ridge

EXEMPTION OF STATIC ELIMINATION DEVICE FROM RADIOISOTOPE APPLICATION

SYMBOL: OI:PCA

Reference is made to your memorandum of June 4, 1954, regarding the proviso attached to the exemption of the static eliminator that "This exemption shall not apply to any sale to, or use by, any person under the age of 18 years."

We did not and still do not concur in this limitation either in principle or as a practical matter. It is unlikely that any benefit will accrue from the limitation and yet it could work a hardship on the manufacturer, distributors, retailers, and ultimate users of the device.

Particular objection is made to the words "or use by." Essentially this provision would subject a person to possible criminal prosecution for violation of federal regulations if he permitted a member of his family under the age of 18 to clean a single photographic negative with the brush.

Further, even though it is desirable to prevent children from obtaining possession of the brushes, we do not understand how the present limitation will achieve this result. Sale or use would have to be limited to customers who will use the brush where there are no children.

If the Isotopes Division takes no positive steps for enforcement of the proviso, but merely investigates alleged violations, it could be argued by persons outside the AEC that we were negligent in failing to enforce the limitation, especially since it was considered sufficiently important to include in the regulations. On the other hand, if the limitation is not sufficiently desirable to warrant positive enforcement it should not appear in the regulations. A practice of publishing regulations with no intent to enforce them could subject the AEC to sharp criticism.

It is our opinion that the proviso is undesirable, and from a realistic viewpoint, is unenforceable. We recommend deletion of the limitation at an early date.

RECEIVED

Paul C. Aebersold

1184454

cc: Assistant General Counsel (2)

-3

Pl C. Aebersold, Director, Isotopes Division
Oak Ridge Operations

June 4, 1954

T. R. Jones, Chemistry Branch, Division of Research

EXEMPTION OF STATIC ELIMINATION DEVICE FROM RADIOISOTOPE APPLICATION PROCEDURE.

Reference is made to your memorandum of May 21, 1954, on this subject.

Amendment of section 30.70, radioisotope distribution regulations provides "This exemption shall not apply to any sale to, or use by, any person under the age of 18 years." We understand that the manufacturer may meet this obligation by labeling his device in the manner indicated in the authorization and by confining his sales to persons 18 years of age or over. He might further assure compliance by including notice of the limitation in his advertising and by instructions to distributors and retailers.

The draft of the amendment submitted to the Division of Biology and Medicine gave the age limit as 21 years. They suggested changing the age limitation to 18 years to be consistent with rules of other agencies. The provision was not required by and was not originated by that division.

Preliminary discussions concerning the proposed amendment invariably included questions about the possible hazards to children from ingestion of Po 210. For this reason the restriction was proposed and included. We do not recall any objection to the provision on the basis that it was unreasonable or unusual.

We have the impression from your memorandum that you do not disagree in principle with the limitation. Our understanding is that you are concerned only with questions as to what enforcement steps are incumbent upon the Isotopes Division. We would appreciate being advised if this is not the case.

Limitation of sales of certain commodities to persons over a certain age is not unusual. We think that in general the limitation does not call for action by the Isotopes Division beyond what is indicated in this memorandum and our other correspondence relating to the [illegible], and to investigation by the Isotopes Division of alleged violations.

Whether any further steps of a preventive nature should be taken is a matter you may wish to decide after consideration of all relevant factors including administrative feasibility and availability of funds.

cc: Claus
Lowenstein
Hiestand, ORO

Chemistry Bio & Med. Gen. Counsel
Jones:lha

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1184453

FICE OF ASSISTANT GENERAL COUNS...

ROUTING SLIP

1	C.C.McNabb		~~R.G.Johnson~~
	~~[illegible]~~		D.L.Oakley (City Adm. Bldg.)
	J.F.Hennessey		K.D.McCasland (City Adm. Bldg.)
	A.B.Gomez		M. Barclay
2	O.S.Hiestand	3	Files
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	J. C. Winkles		Patent Branch

REMARKS:

Have discussed this with Cobb & Hutton who are working on a reply. I believe this is a very inadequate memo on the subject (1) it completely omits reference to sellers other than

FROM:

DATE: JUN 14 1954

1184454

manufacturers, (2) does not cover users, and (3) specifies a very unsound position on enforcement.

I understand PCA was quite disturbed about this restriction being included.

Sparks

1184455

In Reply
Refer to: OR:KK

Oak Ridge, Tennessee
June 1, 1954

Carbide and Carbon Chemicals Company
Post Office Box P
Oak Ridge, Tennessee

Attention: Dr. C. E. Larson, Director
Oak Ridge National Laboratory

Subject: RADIOISOTOPES FOR DRUG APPLICATIONS

Gentlemen:

At the May 7, 1954, meeting of our Advisory Medical Committee in Washington discussions were held with representatives of the Federal Food and Drug Administration concerning radioisotopes distributed by the Oak Ridge National Laboratory which ultimately may be used as drugs.

As you are doubtless aware, Abbott Laboratories has obtained Effective New Drug Applications for Phosphorus 32 and Iodine 131 covering use of these materials in human beings. Under Federal Food and Drug Administration regulations it appears that distribution of Phosphorus 32 and Iodine 131 for drug purposes should not be restricted to holders of Effective New Drug Applications.

The Atomic Energy Commission has maintained the view, and apparently the Federal Food and Drug Administration now concurs, that Carbide and Carbon Chemicals Company would not be required to submit a New Drug Application for Phosphorus 32 and Iodine 131. After discussion with the General Counsel of the AEC and the FDA and after informal discussion with representatives of the Food and Drug Administration, it appears that our proposed plan of handling such shipments for drug purposes will be satisfactory. The Commission has proposed to:

1. Modify the existing label used on ORNL shipments by adding the words "pharmaceutically unrefined"

2. Include with each shipment destined for drug purposes a brief statement by the Atomic Energy Commission reading as follows:

   "Additional tests or processing required to make this product pharmaceutically acceptable:

118445b

(a) for oral administration -- radiochemical purity, precise calibration of doses.

(b) for injection -- radiochemical purity, precise calibration of doses, sterilization."

I realize that the addition of the above information will cause some difficulty in the shipment of isotopes, but am convinced that we have no alternative but to comply with the regulations of the Food and Drug Administration. Your cooperation in making these changes will be greatly appreciated.

In order to be better informed on the actual practices in preparation of isotopes, Commissioner J. L. Harvey of the Food and Drug Administration requested for his information additional details concerning:

1. The Isotopes Division review of medical applications and the degree of experience usually required before allocation.

2. A resume of the procedures and tests carried out by ORNL in processing and preparing Phosphorus 32 and Iodine 131 for shipment.

The Isotopes Division is preparing the information requested by Commissioner Harvey and is already assembling the statement of procedures in reviewing medical applications. They have requested, however, that the Laboratory prepare the resume requested under item 2 in order to be sure that an accurate statement is provided to the Food and Drug Administration. I would appreciate your cooperation in providing this resume at an early date, if convenient. Commissioner Harvey will greatly appreciate our early compliance with his request.

Very truly yours,

Kenneth Kasschau
Director
Research and Medicine Division

cc: C. E. Center
M. H. Woodruff
P. C. Aebersold

COPY

1184457

T. R. Jones, Chemistry Branch, Division of Research, Washington

May 21, 1954

Paul C. Aebersold, Director, Isotopes Division, Oak Ridge

EXEMPTION OF STATIC ELIMINATION DEVICES FROM RADIOISOTOPE APPLICATION PROCEDURE

SYMBOL: OI:PCA

Reference is made to AEC 398/9 providing for amendment of section 30.70 of radioisotope distribution regulations so as to exempt static elimination devices from the requirements of Section 30.20 to 30.53.

The last sentence of this amendment provides that "This exemption shall not apply to any sale to, or use by, any person under the age of 18 years." This office had originally considered such a limitation, but discarded it as unworkable and unenforceable. Initial sales can probably be restricted to persons 18 years or older, but to restrict further sales, transfers, and use to such persons would be a formidable problem, both from the viewpoint of vendors and the Isotopes Division.

It is our understanding that the Office of the General Counsel and the Division of Biology and Medicine believe that such a restriction is necessary. We shall appreciate advice as to what steps the Isotopes Division should take to ensure that this provision is observed and enforced both at the vendor and the user level. If the proviso is unenforceable we would recommend its deletion at an early date.

Paul C. Aebersold

CC: Mr. O. S. Milstead, ORO
Mr. R. Lowenstein, Washington
Dr. C. L. Dunham, Washington

RECEIVED

1184458

APR 1 5 1954

Legal Files

Lee M. Hydeman

MEETING WITH WILLIAM GOODRICH, ASSISTANT GENERAL COUNSEL, FOOD AND DRUG ADMINISTRATION, APRIL 8, 1954

On April 8, 1954, Mr. Robert Lowenstein, Mr. Goodrich and the writer met at Mr. Goodrich's office. The purpose of this meeting was to informally determine the Food and Drug Administration's position regarding possible regulation by FDA of sale by Union Carbide and Carbon of radioisotopes.

Mr. Goodrich stated that he did not feel that FDA would attempt to require Carbide to file new drug applications in order to continue its sales of radioisotopes if AEC agrees to require Carbide to affix suitable labels and to include with its shipments of isotopes directions for proper preparation of drugs utilizing the isotopes. Mr. Goodrich stated that FDA could effectively regulate isotope drug sales by secondary commercial suppliers. However, he advised that it would be extremely difficult for FDA to assure proper isotope drug preparation by hospitals and institutions supplied isotopes by Carbide.

Mr. Lowenstein advised Mr. Goodrich that he would contact the Isotopes Division, Oak Ridge, in order to determine whether they might have any objections to affixing such labels and including such directions in a booklet to accompany Carbide's shipments of isotopes.

After the meeting, Mr. Lowenstein advised Mr. Jones and Mr. Miestand of the foregoing.

CC: T. Raymond Jones, Division of Research
Orris S. Miestand, Jr., ORCO

RECEIVED

1184459

APR 9 1954

William Mitchell, General Counsel,
Washington

J. W. Ould, Jr., Assistant General Counsel,
Oak Ridge Operations

AMENDMENT OF RADIOISOTOPE DISTRIBUTION REGULATIONS REVISING AUTHORIZATION-EXEMPT QUANTITIES

SYMBOL: MC:OSH

Enclosed is a copy of a memorandum from the Manager, ORO, to the Director of Research, with enclosure, submitting a proposed staff paper and amendment to the Radioisotope Distribution Regulations to revise and expand "authorization-exempt" quantities of radioisotopes.

The language of the proposed revisions to the regulations (Appendix B of the enclosure) was concurred in by this office. We have also reviewed the proposed staff paper and concurred in the recommendation made therein.

J. W. Ould, Jr.

Enclosure:
As stated above

Hiestand:mp

Oak Ridge
General Counsel
Office of Assistant
APR 9 - 1954
DISPATCHED

ISOTOPES PROGRAM - 3

OFFICE	MC	MC				
SURNAME	Hiestand	Ould	1184460			
DATE	4/8/54	APR 9 1954				

STANDARD FORM NO. 64

Office Memorandum • UNITED STATES GOVERNMENT

TO : T. H. Johnson, Director, Division of Research, Washington

DATE: April 1, 1954

FROM : S. R. Sapirie, Manager, Oak Ridge Operations

SUBJECT: AMENDMENT OF RADIOISOTOPE DISTRIBUTION REGULATIONS REVISING AUTHORIZATION-EXEMPT QUANTITIES

SYMBOL: OI:GLH

Enclosed is a staff paper for submission to the Commission proposing the revision of authorization-exempt quantities as set forth in the radioisotope distribution regulations.

At present an Authorization for Radioisotope Procurement is not required for the procurement, possession, use, or transfer of radioisotopes in the following amounts: not more than one microcurie of beta and gamma emitters with half-life greater than 30 days and ten microcuries of beta and gamma emitters with half-life no greater than 30 days.

The uses and values of small quantities of radiomaterials have increased appreciably in the past two years. More data is now available on the radiobiological toxicity of radioisotopes than was known at the time current authorization-exempt quantities were established. The revised quantities will prove particularly useful to research workers and yet should maintain adequate safety factors.

The proposed amendment would increase the amounts of certain radioisotopes which may be purchased or otherwise transferred without first obtaining an authorization. However, the values for Strontium 90 and Polonium 210, when not incorporated in a sealed source, have been scaled down. Certain limitations have been placed on the uses of such authorization-exempt quantities of radioisotopes.

This office recommends that the enclosed staff paper be forwarded to the Commission for approval. Distribution of information copies of this staff paper is being made to members of the Isotopes Division's Advisory Committee on Isotopes Distribution.

N. H. Woodruff
for S. R. Sapirie

Enclosure:
Staff Paper

cc: R. W. Cook, Washington, w/encl.
Assistant General Counsel, ORO, w/encl.
T. R. Jones, Washington, w/encl.
J. C. Bugher, Washington, w/encl.

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T. R. Jones, Chemistry Branch, Division of Research, Washington

March 29, 1954

Charles E. Crompton, Assistant Director, Isotopes Division, Oak Ridge

SALES OF RADIOISOTOPES BY AEC NATIONAL LABORATORIES AS AFFECTED BY FOOD AND DRUG REGULATIONS

SYMBOL: OI:GLH

Enclosed is a copy of minutes of the Ad Hoc Committee meeting, February 23, 1954, and a copy of a letter from Mr. W. B. Rankin, dated March 16, 1954. These minutes appear to be a satisfactory account of our Committee meeting. After you, Haggerty and Hydeman have reviewed the minutes, they should be returned to Mr. Rankin with any corrections.

You will recall that Food and Drug representatives expressed the opinion that AEC National Laboratories, particularly ORNL, are violating the FFD&C Act and regulations by shipping radioisotopes intended for human use to persons not possessing an "effective new drug application." Although this opinion does not appear in the minutes, the attached letter from Mr. Rankin states that Carbide is considered a manufacturer required to obtain a new drug application if it sells for drug uses.

Our position in this matter is as follows:

(1) The AEC National Laboratories are merely distributing Government-owned radioisotopes for the AEC pursuant to provisions of the Atomic Energy Act and AEC approvals under contracts for operation of the AEC facilities. In other words, what Carbide does or does not do is no different than if the AEC undertook to make such distributions directly with its own personnel. It is doubtful, therefore, that AEC National Laboratories, in performing this distribution function, are bound by provisions of the FFD & C Act. The Atomic Energy Act provides for distribution of by-product materials by AEC for medical use and expressly authorises the Commission to establish, by regulation or order, standards to govern the possession and use of such materials as the Commission considers necessary to protect health. In event of conflict of jurisdication, therefore, it would appear that the Atomic Energy Act with its express provisions for distribution of radioisotopes for medical therapy in accordance with health standards established by the AEC may prevail over the FFD&C Act.

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Carbide's function, of course, is to make distribution to those persons holding valid AEC authorization to possess and use. If there is a question as to who may possess and use radioisotopes, so far as the laboratory is concerned, this is a matter which should be resolved in terms of AEC's authority to permit possession and use. Once the authorization holder applies to Carbide for approved material, Carbide has no discretion to reject the order if ORNL has the radioisotope available or can make it available.

(2) Even though we believe ORNL is not subject to Food and Drug regulations it is complying substantially therewith. Where drug use is indicated, ORNL obtains Form AEC-465 in which the recipient certifies that he will use the material for investigational use. Shipments are clearly marked with a label, which the Food and Drug Administration has indicated as satisfactory, stating:

> "If intended for drug purposes, Caution: for manufacturing, processing, or repacking in the preparation of a new drug, limited by Federal law to investigational use, unless the recipient holds an effective new drug application."

If a person certifies falsely as to the intended use, obtains clearly labeled material and uses it in a manner other than as indicated on the label, it would appear that the shipper has complied with lawful requirements and the recipient is at fault.

ORNL is the AEC's distributor to make radioisotopes available pursuant to the Atomic Energy Act, and we do not see how we can restrict the right of "authorized" persons from coming to AEC facilities to obtain materials. As far as exempt quantities are concerned, there are no AEC restrictions on procurement. Many non-exempt quantities of radioisotopes are obtained on general authorizations. In all cases ORNL has been instructed to use the approved caution label. Once AEC has approved the possession and use, Carbide instructions are to distribute. We do not see where, under these circumstances, that Carbide (or AEC) should be considered a manufacturer of drug items, and believe it would be burdensome and discriminatory under the Atomic Energy Act to follow the suggestions in Mr. Rankin's letter.

Dr. R. G. Smith, Division of Medicine, FDA, in a recent telephone conversation, indicated that the Food and Drug Administration would clarify the meaning of Item 1, page 2, of Mr. Rankin's letter regarding the proposal that ORNL file a new drug application. I indicated that it was our opinion that the Food and Drug Administration did not have jurisdiction over an operation such as

that of ORNL; and stated that we would not instruct ORNL to file a new drug application. I asked if there was any precedent for a contractor, such as ORNL, distributing Government-owned materials, obtaining an effective new drug application. I suggested that ORNL might consider adoption of a different label and we would appreciate information as to the type of labeling they consider adoption of a different label and we would appreciate information as to the type of labeling they consider to be desirable.

Dr. Smith stated that FDA would furnish the requested clarification and information. Upon receipt of this further information, copies of the correspondence will be forwarded to you.

Original Signed By
Charles E. Crompton
Charles E. Crompton

Enclosures:
1. Minutes
2. Cy. ltr. fm. Mr. Rankin, dtd. 3/16/54

cc: Assistant General Counsel, w/cy. ltr.

Hutton/rmj/jct

C O P Y

DEPARTMENT OF
HEALTH, EDUCATION, AND WELFARE
FOOD AND DRUG ADMINISTRATION
Washington 25, D. C.

March 16, 1954

Dr. Charles E. Crompton
Assistant Director
Isotopes Division
Atomic Energy Commission
Oak Ridge, Tennessee

Dear Dr. Crompton:

We appreciate the list of secondary distributors and hospital users of radioactive Iodine and Phosphorus for medical use which accompanied your letter of March 5, 1954.

Since the meeting of the Ad Hoc Committee last month, we have given further study to the distribution of radioisotopes for therapeutic and diagnostic use. We are summarizing the views of the Food and Drug Administration in this memorandum even though this repeats some discussions of matters already covered in the committee; but at least one of the possibilities discussed below has not been given detailed consideration since you became a member of the committee.

Traditionally, hospitals are institutions which use medication in finished pharmaceutical forms. While some of the larger hospitals do have manufacturing units associated with them, and have retail pharmacies where some compounding is performed, these conditions do not alter the fact that the hospital per se is not a manufacturing establishment; in general, where complicated production procedures are required, the hospital relies upon a pharmaceutical manufacturer to produce drugs under appropriate control.

This basic fact may simplify our search for a practical method of regulating the distribution of isotopes. In searching for a suitable procedure for getting into the hands of the hospital a finished pharmaceutical that is ready for use without manufacturing operations, we should look not to the hospital but rather to the manufacturer for primary compliance with the new drug provisions of the Food, Drug, and Cosmetic Act.

So far as drug production is concerned, the manufacturer of radioisotopes is Union Carbide and Carbon Chemicals Company, or the secondary distributor who purchases from it, or both.

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If Union Carbide and Carbon Chemicals Company (UC&C) does not wish to engage in drug manufacturing, it could sell isotopes to secondary distributors who will produce a pharmaceutically acceptable finished product. Under this type of distribution, UC&C would distribute to the 10 secondary distributors listed with your letter of March 5 and any hospitals who, in addition to performing the traditional role of hospitals, wish to engage in a second enterprise, the manufacture and distribution of drugs. The bulk shipments of radioisotopes would go forward to these secondary distributors under the type of labeling already agreed to between the Atomic Energy Commission and the Food and Drug Administration. It would be the responsibility of the secondary distributors to secure effective new drug applications before further distributing the isotopes.

Under this type of distribution, we imagine that relatively few of the 88 hospitals who have been receiving regular shipments would continue to receive shipments; the bulk of the drug distribution soon would be handled by a few secondary distributors.

On the other hand, if UC&C prefers to continue to make radioactive isotopes available to a large number of hospitals for therapeutic and diagnostic use, we believe that the Atomic Energy Commission and the Food and Drug Administration should recognise that the firm is engaging in drug distribution and should ask it to file a new drug application covering the manufacture, labeling and distribution of each isotope which it distributes in this manner. This application of UC&C could cover either of two types of drug distribution:

1. If the company wishes to continue to ship pharmaceutically unrefined lots of radioisotopes to secondary distributors and hospitals, it could comply with the requirements of the new drug section of the Food, Drug, and Cosmetic Act by filing an application which provided, among other things, for adequate directions in the labeling of the bulk merchandise for

   a. Preparing a finished, pharmaceutically acceptable drug; and

   b. Properly using this drug in medicine.

   Under this type of distribution, hospitals performing the traditional hospital function would not need to have an effective new drug application to secure bulk shipments. Secondary distributors (including hospitals acting as distributors) would need effective new drug applications before shipping isotopes which they refine to another ultimate user.

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2. If the company prefers to ship finished pharmaceuticals, it could file a new drug application covering the preparation of such drugs and providing for adequate directions in the drug labeling to permit the receiver to use the radioisotopes properly.

So that we will be in a better position to discuss the status of isotopes with hospital users, we would appreciate your letting us know in the near future which type of distribution UC&C wishes to make.

The above discussion applies only to radioisotopes being distributed for therapeutic and diagnostic purposes. We recognize that an isotope, other than Iodine 131 and Phosphorus 32 which still is being used for genuine investigational purposes to establish its safety, will continue to go direct from UC&C to investigators with the investigational use legend already being employed. However, we can anticipate a time when the findings of the investigators indicate the desirability of employing the isotope for therapeutic or diagnostic purposes. At that time UC&C would again need to make the same decision with regard to this isotope that it needs to make today with regard to Iodine and Phosphorus; that is, does it wish to be a manufacturer of basic chemicals or does it wish to engage in the drug business and file a new drug application covering the manufacture, labeling, and distribution of the new isotope?

Dr. Smith and I considered the advisability of telephoning you to discuss these views but we realized that the discussion is so complex it would be difficult to present our thoughts clearly by phone. If after reading this letter you find that there are still unanswered questions, feel free to get in touch with us by telephone or letter.

Sincerely yours,

/s/ W. B. Rankin, Assistant Director
Division of Field Operations

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