



December 13, 1984

Food and Drug Administration
Washington DC 20204

FOI Services, Inc.

12315 Wilkins Avenue

Rockville, MD 20852-1877

DOCUMENT # 40964

Re: FOI No. F84-35734 Control No. 40964

DEC 18 1984

Dear Sirs:

In response to your request of Nov. 6, 1984 for information on the color additive petition filed for Chromium-Cobalt-Aluminum Oxide for the coloring of sutures.

☒ Enclosed are the records you requested.

☐ We have searched our files and find no responsive information.

☐ Your request is also being referred to one of our component offices.

☒ As you will note, minor deletions of material have been made in the records furnished to you. In the judgement of the Food and Drug Administration the information deleted does not fall within the scope of your request and, in any case, is not required to be disclosed under the Freedom of Information Act. If, however, you do desire to review the deleted material, please make an additional request. If the agency should then deny you this information you would have the right to appeal such denial to the Department of Health and Human Services. Any letter of denial will tell you how to make this appeal.

Sincerely yours,

*Rudolph Harris*Division of Food and Color Additives
Center for Food Safety
and Applied Nutrition

Enclosure

DAVIS & GECK

CYANAMID

DIVISION OF AMERICAN CYANAMID COMPANY

DANBURY, CONNECTICUT

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January 31, 1964

Mr. David J. Miller
Office of the Commissioner
Food and Drug Administration
Department of Health, Education and Welfare
Washington 25, D. C.

CAP 12

Dear Mr. Miller:

Accompanying this letter are three copies of a petition requesting the listing by the Commissioner of the color additive chromium, cobalt, aluminum oxide pigment for use in or on surgical sutures made of linear polyethylene. Reference is made to my letter to you of December 19, 1963, transmitting a check for \$10,400 for payment of fees for proposed petitions. Receipt of this check was acknowledged by Mr. F. E. McLaughlin in his letter to me of January 2, 1964. The \$2600 fee for filing of the attached petition is to be taken from this \$10,400 deposit.

Very truly yours,

David Kaufman

David Kaufman, PhD.
Technical Director

DK:jm
Enclosures

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January 31, 1964

Name of Petitioner: Davis & Geck Division, American Cyanamid Company

Post Office Address: Danbury, Connecticut

Name of Color Additive and Proposed Use - Chromium, cobalt, aluminum
oxide pigment for coloring
linear polyethylene sutures
for use in general surgery.

Commissioner of Food and Drugs
Food and Drug Administration
Department of Health, Education and Welfare
Washington 25, D. C.

Dear Sir:

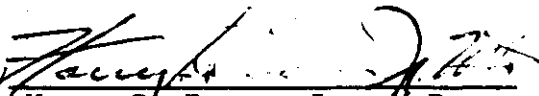
Petitioner submits this pursuant to Section 706 (b) (1) of the Federal Food, Drug and Cosmetic Act requesting listing by the Commissioner of the color additive chromium, cobalt, aluminum oxide pigment as suitable and safe for use in or on surgical sutures made of linear polyethylene, subject to the conditions that the composition be that of the product designated by Code No. F 5272 of the Ferro Corporation of Cleveland, Ohio, and that the concentration of pigment in the polymer be 2% or less by weight.

Attached hereto in triplicate and constituting a part of this petition is the information required by Title 21 Subchapter A Part 8 Subpart A Section 8.4 of the Regulations of the Food and Drug Administration as published in the Federal Register for Saturday, June 22, 1963.

The prescribed fee of \$2,600 for admitting the color additive to listing is covered by the funds deposited with the Food and Drug Administration by letter and check of December 19, 1963, acknowledgment of which has been received.

Yours very truly,

Davis & Geck Division
American Cyanamid Company

By 
Harry D. Evans, Jr., M.D.
Medical Director

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AMERICAN CYANAMID COMPANY

SIGNATURE AUTHORIZATION NO. 278

DAVIS & GECK DIVISION

1. Pursuant to The General Resolution for Signatures on Contracts, adopted by the Board of Directors of American Cyanamid Company on February 17, 1948, as amended, the person named below is hereby authorized to sign on behalf of said Company to the extent indicated:

Applications and other documents required to be filed either (i) with any Federal or State Agency, or (ii) with any foreign government, relating to the production, registration, or sale of products manufactured or sold by the Davis & Geck Division of said Company, as follows:

Name and Position

Extent of Authorization

HARRY D. EVANS, JR.
Government Registrations
Davis & Geck Division

All such applications
and other documents.

2. Unless sooner modified or terminated, this authorization shall continue in effect as to each person named herein so long as such person continues to hold the position indicated above.

3. This authorization shall not be construed as modifying or terminating any previous authorization made pursuant to The General Resolution for Signatures on Contracts, except that the following authorization is hereby terminated:

Signature Authorization No. 263, effective
the 1st day of June, 1962.

IN WITNESS WHEREOF, we have signed this instrument
effective the 1st day of November, 1962.

Attested and filed in the
Office of the Secretary
on December 28, 1962

s/ R. O. Roblin
Vice President

s/ R. C. Swain
Vice President

s/ H. W. Wilson
Assistant Secretary

(SEAL)

(A conformed copy of the above Signature Authorization
will be furnished if requested)

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Subpart A

1. Nature and Manufacturer of Color Additive.
The color additive used to color linear polyethylene surgical suture material is an inorganic pigment composed of chromium, cobalt and aluminum oxides. It is manufactured by the Ferro Corporation, Cleveland, Ohio, and is designated by their code No. F5272.
2. Composition, Physical and Chemical Properties of the Color Additive.
The composition, physical and chemical properties of pigment F5272 were sent to Mr. D. J. Miller of the FDA by the Ferro Corporation on February 4, 1963.
3. Manufacture of the Linear Polyethylene Fiber.
The linear polyethylene fiber is manufactured by Reeves Brothers, 54 Worth Street, New York 13, New York. They obtain the pigment from the Ferro Corporation and blend it with the polyethylene resin prior to a hot melt extrusion. The melt is heated to 500°-550°F and is extruded through a fixed orifice. The filaments are cooled in air or water, oriented by cold drawing and set by annealing in a hot water bath. This produces a strong, dimensionally stable filament whose colorant is firmly embedded in an inert, nontoxic matrix.
4. Identification of the Pigment in the Suture Material.
The pigment in each lot of blue linear polyethylene is identified qualitatively by Ultraviolet Emission Spectrography, with colorless linear polyethylene as a control. This standard elemental analysis procedure shows typically that chromium, cobalt and aluminum are the major inorganic elements in the colored suture material. The analysis also shows minor amounts of boron, calcium, silicon and titanium. The other elements are detected only in trace quantities or not at all. A copy of the results of an elemental qualitative spectrographic analysis of size 000 blue linear polyethylene is presented on Pages 3, 4 and 5 which follow.
5. Biological Properties.
Biological studies (Subpart D) have shown that the chromium, cobalt, aluminum oxide pigment in blue linear polyethylene is inert, nontoxic and nonirritating when the fiber is used as a surgical suture.

Page 3
STAMFORD RESEARCH LABORATORIES

RESEARCH SERVICE DEPARTMENT REPORT

No. UVE-

D 26

TO <i>Arthur Flick</i>	DEPT. <i>Physics & Chem</i>	ROOM NO.
FROM <i>ULTRAVIOLET SPECTROSCOPY</i>	DATE REPORTED <i>1 Nov. 1963</i>	
MATERIAL <i>Linear Polyethylene</i>	TEST <i>QUALITATIVE SPECTROGRAPHIC ANALYSIS</i>	
CHARGE NO. <i>300-11 (Flick)</i>	DATE SUBMITTED <i>31 Oct. 1963</i>	
WORK REPORTED BY <i>Wm. L. Dutton</i>	NOTEBOOK REFERENCE <i>54107-178</i>	

The ranges for qualitative estimates are indicated as follows:

8 = 100 to 1.0%	6 = 1.0 to 0.01%	4 = 100 to 1.0 ppm.	2 = 1.0 to 0.01 ppm.
7 = 10 to 0.1%	5 = 0.1 to 0.001%	3 = 10 to 0.1 ppm.	1 = less than 0.1 ppm.

X _____ = not detected at _____.

< _____ = might be detected at < _____ by special procedure.

Estimates are based on the samples as submitted, unless otherwise noted as "F".

F = wt. residue/wt. sample.

SAMPLES			Plate No.	U.V. No.
A	3-0 Blue	F=0.4	1 Nov. 63 (A)	14,699
B	3-0 White	F=0.3	"	14,750
C				
D				

SAMPLE					SAMPLE					SAMPLE				
El.	A	B	C	D	El.	A	B	C	D	El.	A	B	C	D
Al	6	4			Hf					Pt	X4	X4		
Sb	X4+	X4+			Ir					K	<6	<6		
As	X5	X5			Fe	4+	4			Rh				
Ba	<6	<6			Pb	X4+	X4+			Si	6	6-		
Be	X2	X2			Li	<5+	<5+			Ag	2+	2+		
Bi	X4	X4			Mg	4+	3+			Na	<5	<5		
B	6	X4			Mn	4	4			Ta	X6	X6		
Cd	4+	X4+			Hg	X4	X4			Te				
Ca	5+	<5+			Mo	X4	X4			Sn	X4+	X4+		
Cr	7	4+			Ni	X4	X4			Ti	5	X4		
Co	7+	X4			Nb	X4+	X4+			W	X5	X5		
Cu	4	4-			Os					V	X4	X4		
Ge	X4	X4			Pd	X4-	X4-			Zn	X5	X5		
Au	X4+	X4+			P	X5+	X5+			Zr	X5	X5		

By Special Procedure: -

Ce					In					Sc				
Cs					La					Sr				
Dy					Lu					Tb				
Er					Nd					Tl				
Eu					Pr					Th				
F					Re					Tm				
Gd					Rb					U				
Ga					Ru					Yb				
Ho					Sm					Y				

Concentration = Estimate x F

Symbols Used in Reporting Regular
QUALITATIVE SPECTROGRAPHIC ANALYSES

by Wm. L. Dutton

Symbol	Meaning
<	"less than" and "not detected", used preceding a range symbol digit only. The concentration is less than the logarithmic average of the range of the symbol digit, which is also the least detectable amount. The concentration could be zero. Thus "<4" means that the limit of detection is 10 ppm, the logarithmic average of the range for symbol "4". If the element were present in a concentration less than this it could not be detected under the conditions used.
X	The element was looked for but not detected. The least detectable concentration is below about 1 ppm.
+	Following a range symbol digit only. The concentration is the logarithmic average of the portion of the range greater than the logarithmic average of the range. For instance "4+" indicates that the concentration is about 33 ppm.
-	Following a range symbol digit only. The concentration is the logarithmic average of the portion less than the logarithmic average of the range. For instance, "4-" indicates that the concentration is about 3.3 ppm.

No Symbol The element was not looked for, but can be, if requested.

1 to 8 Each range symbol digit is 3 more than the logarithm of the logarithmic average of the range expressed in ppm.

Since the range symbol digits are logarithmic, the difference between any two is the logarithm of the ratio of their concentrations and has greater accuracy than either concentration.

The limits of each symbol digit range can be expressed by multiplying the logarithmic average of the range by $10^{\pm 1}$. Thus the concentrational limits of the range for symbol digit "3" = $1 \times 10^{\pm 1}$ ppm or 10 to 0.1 ppm.

When the report is not based on the "sample as submitted", or the amount charged in the electrode is less than the standard amount, the estimates of concentrations given should be multiplied by the factor, as noted under "Remarks".

"F" is a reduction by heat = gm. per gm.

"FC" is a correction for a less than standard charge.

"FG" is a correction for a reduction by heat when pure graphite powder was added as a vehicle.

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For convenience in applying the above, the complete symbol table follows:

<u>Range</u> <u>Symbol</u>	<u>Concentration</u>	<u>Range</u> <u>Symbol</u>	<u>Concentration</u>
8	100% to 1%	4	100 to 1 ppm
7	10% to 0.1%	3	10 to 0.1 ppm
6	1.0% to 0.01%	2	1.0 to 0.01 ppm
5	0.1% to 0.001%	1	Less than 0.1 ppm

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Subpart B

1. Amount of Pigment Proposed for Use.

The pigment concentration employed for coloring linear polyethylene sutures is of the order of 1% by weight. Because the pigment is locked permanently in a water insoluble polymer and is also insoluble in water in its own right, there are no contraindications to adding considerably more pigment, if necessary. However, it is believed that adequate color intensity can be obtained with pigment concentrations of the order of 2% or less. The sole purpose of the pigment is to color the normally transparent linear polyethylene so that it may be visible at all times in the surgical operative field.

Subpart C

1. Determination of Pure Pigment.

No procedure for determining pure color is included in this petition because Davis & Geck does not obtain any pigment from the Ferro Corporation but only obtains an extruded and colored linear polyethylene fiber from a textile manufacturer. The petitioner can only check the identity of the pigment in the colored fiber we purchase and market by chemical and spectrographic analyses on the colored fiber or its pigment after ashing the fiber.

2. Description of Methods to Determine the Pigment Content of the Suture Material.

Each lot of blue linear polyethylene suture material is assayed for pigment content by ashing the fiber; the pigment is then assayed for its major components (chromium, cobalt, aluminum) by a quantitative chemical method.

(a) Ash Procedure

- (1) Samples of blue and clear linear polyethylene suture material are dried for 2 hours at 50°C and then allowed to come to equilibrium overnight in a dessicator.
- (2) Weigh at least 0.2 grams of each sample and place them in 25 ml. tared, porcelain crucibles which have been previously heated to 600°C, dried to a constant weight.
- (3) Place the crucibles with their contents into a muffle furnace at 200°C.
- (4) Raise the furnace temperature to 500°C and maintain it for 15 minutes.
- (5) Turn the furnace off and allow the crucibles to cool to 200°C before transferring them to a dessicator to come to equilibrium overnight.
- (6) Remove the crucibles from the dessicator, weigh and calculate the percent ash residue.

Calculation

$$\text{Ash, percent} = \frac{\text{weight of residue}}{\text{weight of sample}} \times 100$$

% Pigment

Blue linear polyethylene - % Ash

Clear linear polyethylene - % Ash

Difference = % Pigment in fiber

By the above method of ash analysis the blue linear polyethylene fibers which are currently being marketed have shown a pigment content of $0.83\% \pm 0.06\%$ of the weight of the fiber.

(b) Quantitative Chemical Analysis of the Ash Residue of Blue Linear Polyethylene.

The ash residue obtained from the blue linear polyethylene is analyzed by quantitative chemical methods to determine the composition of its pigment. A sample of 000 blue linear polyethylene was analyzed for the composition of its pigment and the results are reported below as the percent metal present.

<u>Sample</u> <u>Identification</u>	<u>Chromium</u> <u>as % Cr</u>	<u>Cobalt</u> <u>as % Co</u>	<u>Aluminum</u> <u>as % Al</u>
Pigment from 000 sample	22.6	21.7	17.0

All the above values are based upon the pigment obtained by the ignition of the 000 blue linear polyethylene.

Given below are the quantitative chemical methods used to obtain the percent composition of the color additive.

ANALYSIS OF PIGMENT FROM POLYETHYLENE FILAMENTDetermination of Chromium, Cobalt and AluminumI. Principle of the Method

A sample of pigment is obtained by ashing the polyethylene filament. A portion of the pigment sample is digested with perchloric acid to dissolve chromium and cobalt, and the two metals are then separated by precipitation of the cobalt with caustic under oxidizing conditions. After acid dissolution cobalt is determined by potentiometric titration with ferricyanide. The chromate in the filtrate is titrated with ferrous iron.

For the determination of aluminum, a sample of pigment is fused with sodium peroxide and leached with water. The aluminum in the aqueous phase is separated by precipitation as aluminum hydroxide, which is then dissolved and titrated with EDTA.

II. Preparation of Pigment SampleApparatus

1. Dishes, platinum.
2. Sieve, 70-mesh.
3. Furnace, controllable at temperatures up to 500°C.

Procedure

Prepare sufficient pigment for the analysis (about 1 g.) by ashing several portions of polyethylene filament as follows: Put about 20 g. of filament in a platinum dish and place in a muffle furnace at 200°C. Gradually increase the temperature and ignite at 500°C. for one hour. Pass the combined ash through a 70-mesh sieve and blend thoroughly.

III. Determination of Chromium and CobaltA. SeparationApparatus

1. Fume eradicator and reflux head for 250-ml. flask. Available from G. Frederick Smith Chemical Co. (Item nos. 184 and 181). Assemble as shown on page 103 of the 1963 Price List catalog, G. Frederick Smith Chemical Co.
2. Vacuum filtration assembly fitted with a fritted glass filter crucible of medium porosity.

~~9~~Reagents

1. Nitric acid, concentrated.
2. Perchloric acid, 70%.
3. Sodium hydroxide, 50%, 10% and 5% solutions.
4. Sodium peroxide, calorific grade.
5. Hydrogen peroxide, 30%.

Procedure

Weigh about 0.15 g. of the pigment (as prepared in Section II above) into a 250-ml. Erlenmeyer flask, add 10 ml. of concentrated nitric acid and 15 ml. of perchloric acid (Caution: observe recommended safety precautions for handling perchloric acid). Place a fume eradicator-reflux head assembly over the flask and digest on a hot plate until the residue has no dark color. Cool, add 50 ml. of water and boil for several minutes. Filter through a No. 42 Whatman paper and wash the residue with small portions of hot water until free of acid. Discard the residue.

To the filtrate (filtrate A), add 50% sodium hydroxide until the solution is only slightly acid. Transfer the solution slowly, with stirring, into a beaker containing an equal volume of 10% sodium hydroxide solution and 5 g. of sodium peroxide. (Caution: add the sodium peroxide to the cold sodium hydroxide solution just before use).

Add 2 to 3 g. of sodium peroxide and boil for about five minutes, adding three 0.5-ml. portions of hydrogen peroxide. Allow the precipitate to settle and filter through a fritted glass filter crucible. Rinse the beaker and wash the precipitate (precipitate B) with hot 5% sodium hydroxide until the washings are colorless. Reserve the filtrate (filtrate C).

Stand the crucible with precipitate B in a 150-ml. beaker containing about 15 ml. of water, and add 10 ml. of concentrated nitric acid to the crucible. Cover the beaker with a watch glass and digest until the precipitate has dissolved. Wash the solution into a 400-ml. beaker (rinse the crucible by drawing a small amount of water through it). Carry this solution through the same precipitation and filtration procedure used above, beginning with: "To the filtrate (filtrate A), add 50% sodium hydroxide". Combine the filtrate from this second separation (filtrate D) with filtrate C above and reserve for the titration of chromium. Reserve the precipitate from the second separation (precipitate E) for the titration of cobalt.

~~3~~B. Measurement of ChromiumReagents

1. Sulfuric acid, concentrated and 1:1
2. Silver nitrate, 2.5% solution
3. Ammonium persulfate, 10% solution. Prepare just before use.
4. Ceric sulfate, 0.1 N, standardized.
5. Ferrous sulfate, 0.1 N, standardized vs. ceric sulfate solution just before use.
6. Ferroin indicator. 1,10-phenanthroline-ferrous sulfate, 0.025 M. Available from G. Frederick Smith Chemical Co. (Item no. 165).

Procedure

To the combined filtrates C and D, carefully add 1:1 sulfuric acid with stirring until the solution is just acid; then add 5-6 ml. of concentrated sulfuric acid for each 100 ml. of volume. Heat to boiling and add 2 ml. of 2.5% silver nitrate and 20 ml. of ammonium persulfate solution; continue boiling for 10 minutes. Cool to room temperature, add standard ferrous sulfate solution from a buret until the solution turns blue-green and then add 5 ml. in excess. Add 1 or 2 drops of ferroin indicator and titrate the excess ferrous sulfate with 0.1 N ceric sulfate to the disappearance of the red color.

Calculation

$$\text{Chromium as \% Cr} = \frac{(F \cdot G - H \cdot J) 1.733}{\text{g. of pigment sample}}$$

where: F = ml. of ferrous sulfate solution

G = normality of ferrous sulfate solution

H = ml. of ceric sulfate solution

J = normality of ceric sulfate solution

C. Measurement of CobaltApparatus

1. pH meter, equipped with glass and calomel electrodes. A Beckman Model G instrument is satisfactory.

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2. Potentiometric titration assembly. A magnetic stirrer and a pH meter equipped with platinum and calomel electrodes. A Beckman Model G instrument is satisfactory.

Reagents

1. Eriochrome Black T indicator. Triturate 1 part of Eriochrome Black T (Eastman No. 6361) with 200 parts of ammonium chloride.
2. EDTA solution, 0.025 M, standardized. Dissolve 9.30 g. of ethylenediamine tetraacetic acid, disodium salt (Eastman No. 6354) in one liter of water. Standardize vs. zinc metal (Reference 1).
3. Zinc acetate solution, 0.025 M, standardized. Dissolve 5.49 g. of zinc acetate dihydrate in about 700 ml. of water in a 1000-ml. volumetric flask. Allow to stand a few minutes; if a turbidity develops, add acetic acid dropwise until the solution clears. Dilute to volume and mix. Standardize vs. the 0.025 M EDTA solution.
4. Cobalt nitrate solution, standardized. Dissolve 5.00 g. of cobalt nitrate hexahydrate in water and dilute to one liter. Standardize as follows: Pipet 25.00 ml. into a 250-ml. beaker, add 20.00 ml. of 0.025 M EDTA solution. Using a pH meter, adjust the solution to pH 10 with 1:1 ammonium hydroxide. Add sufficient Eriochrome Black T indicator to give a blue color of moderate intensity. Titrate with 0.025 M zinc acetate solution until the indicator just turns from blue to red.

$$\text{mg. Co/ml (T)} = \frac{(K \cdot L - M \cdot N) 58.94}{P}$$

where: K = ml. of EDTA solution

L = molarity of EDTA solution

M = ml. of zinc acetate solution

N = molarity of zinc acetate solution

P = ml. of cobalt nitrate solution

5. Ammonium citrate solution. Dissolve 200 g. of citric acid in water and add slowly 270 ml. of concentrated ammonium hydroxide. Cool and dilute to one liter.
6. Potassium ferricyanide solution. Dissolve 11 g. of potassium ferricyanide in water, dilute to one liter, and store in an amber bottle. Standardize as follows: Pipet 20.00 ml. into

~~III~~

a 600-ml. beaker. Add 20 ml. of ammonium citrate solution and 80 ml. of concentrated ammonium hydroxide and dilute to about 400 ml. with water. Titrate with cobalt nitrate solution to a potentiometric end point. Calculate the ratio (R) of ml. of cobalt nitrate solution to ml. of potassium ferricyanide solution.

Procedure

Dissolve precipitate E in the same manner as described for precipitate B in Section III, A (Separation of chromium and cobalt).

Boil the solution for a few minutes, cool, and neutralize with concentrated ammonium hydroxide. Redissolve any precipitate by the addition of a few drops of 1:1 nitric acid. Cool the solution in an ice bath.

Measure 25.00 ml. of potassium ferricyanide solution into a 600-ml. beaker. Add 20 ml. of ammonium citrate solution and 80 ml. of concentrated ammonium hydroxide. Transfer the chilled sample solution very slowly, with continuous stirring into the beaker containing the ferricyanide solution. Titrate the excess ferricyanide with cobalt nitrate solution to a potentiometric end point.

Calculation

$$\text{Cobalt as \% Co} = \frac{(Q \cdot R - S) T \times 0.1}{\text{g. of pigment sample}}$$

where: Q = ml. of potassium ferricyanide solution

R = ml. of cobalt nitrate solution equivalent to one ml. of potassium ferricyanide solution

S = ml. of cobalt nitrate solution

T = mg. of cobalt per ml. of cobalt nitrate solution

IV. Determination of Aluminum

Apparatus

1. Crucibles, Armco iron, 50-ml. (Fisher No. 8-050), with lids to fit (Fisher No. 8-055).

Reagents

1. Sodium peroxide, calorific grade.
2. Sodium hydroxide, pellets and 0.5% solution.

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3. Ammonium hydroxide, 1:1.
4. Ammonium chloride, solid reagent and 5% solution.
5. Hydrochloric acid, 1:1.
6. Sulfuric acid, 1:1.
7. EDTA solution, 0.025 M. See Reagents, Section III, C (Measurement of Cobalt).
8. Zinc acetate solution, 0.025 M, standardized. See Reagents, Section III, C (Measurement of Cobalt).
9. Orange IV indicator (Eastman No. 823), 0.2% solution in ethanol.
10. Dithizone indicator (Eastman No. 3092), 0.025% solution in ethanol. Store in a refrigerator.
11. Indicator paper, Alkacid (Fisher No. 14-839).
12. Ethanol, 2B or 95%.
13. Buffer, pH 5.0. Dissolve 60 ml. of acetic acid and 77.1 g. of ammonium acetate in water and dilute to one liter.

Procedure

Weigh about 0.125 g. of the pigment sample (as prepared in Section II above) into an iron crucible containing a thin layer of sodium peroxide. Cover the sample with 3-4 g. of sodium peroxide and add five sodium hydroxide pellets. Fuse the sample by standard procedures (e.g., Ref. 3, page 839).

Cool the crucible, place in a covered 600-ml. beaker and add 350 ml. of cold water. When disintegration of the melt is complete, remove and rinse the crucible and lid. Cover the beaker, boil for three minutes and cool. Filter through No. 1 Whatman filter paper (10.5 cm.) and wash the precipitate with 0.5% sodium hydroxide solution until the washings are colorless. Discard the precipitate. (Refilter if the filtrate is not clear.) Add 1:1 sulfuric acid to the filtrate until just acid to indicator paper. Add 5 g. of ammonium chloride, heat to boiling, and make the solution just alkaline to indicator paper by dropwise addition of 1:1 ammonium hydroxide. Boil for one-half minute and filter while hot through a No. 41 Whatman paper. Rinse the beaker and wash the precipitate well with hot 5% ammonium chloride solution. Discard the filtrate and washings.

Dissolve the precipitate in a minimum of hot 1:1 hydrochloric acid. Add 50.00 ml. of 0.025 M EDTA solution, 3 or 4 drops of Orange IV indicator, and 1:1 ammonium hydroxide until the solution just turns yellow.

Boil the solution for three minutes, cool, and add 1:1 ammonium hydroxide until the solution is again just yellow. Add 10 ml. of pH 5 buffer, dilute with an equal volume of ethanol and cool. Add 8-10 ml. of dithizone indicator and titrate the excess EDTA with 0.025 M zinc acetate to a pink end point.

Carry a blank throughout.

Calculation

$$\text{Aluminum as \% Al} = \frac{(X - Y) Z \times 2.698}{\text{g. of pigment sample in aliquot}}$$

where: X = ml. zinc acetate solution to titrate blank

Y = ml. zinc acetate solution to titrate sample

Z = molarity of zinc acetate solution

V. References

1. F. J. Welcher, "The Analytical Uses of Ethylenediaminetetraacetic Acid", D. Von Nostrand Co., Princeton, N.J. (1958).
2. N. H. Furman (Ed.), "Standard Methods of Chemical Analysis", Sixth Edition, Vol. I, D. Von Nostrand Co., Princeton, N.J. (1962).
3. W. F. Hillebrand and G. E. F. Lundell, "Applied Inorganic Analysis", John Wiley and Sons, Inc., New York, N.Y. (1953).
4. I. M. Kolthoff and P. J. Elving (Eds.), "Treatise on Analytical Chemistry", Part II, Volumes 2 and 8, Interscience, New York, N.Y. (1962 and 1963).

General Analytical Laboratories
January 21, 1964

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3. Methods to Determine and Identify Any Substance Formed in or on the Suture Material Because of the Use of the Pigment.

There is no known chemical combination between the pigment F5272 and the linear polyethylene suture material. The colorant is simply dispersed and embedded in an inert matrix.

These inorganic oxides are unreactive and stable at the 500°-550°F temperature required for the hot melt extrusion of linear polyethylene and have melting or decomposition points ranging from 900°-1999°C.

Subpart D

1. In compliance with Part 8.4, Subpart D, of the Color Additive Regulations, animal investigations were carried out to determine the safety of linear polyethylene sutures colored with pigment F5272 manufactured by the Ferro Corporation.
2. The materials and methods used to determine the safety of blue pigmented linear polyethylene are given below.

- (a) The blue pigmented linear polyethylene sutures used in this experiment were prepared by the method described in Subsection A-3 of this petition. The pigment dispersed in the suture material is Ferro Corporation F5272 and is described in this petition under Subsection A-2. Control suture material was prepared as described in Subsection A-3 but had no pigment added and is referred to as natural linear polyethylene. All sutures were of the size 000 (diameter - .0100 in.). All sutures described in this report were packaged separately and sterilized by gaseous ethylene oxide. This procedure is given below:

Needled sutures were wound into small coils and inserted into inert plastic envelopes. The unsealed envelopes were placed in a sterilizer where the package and suture were exposed to ethylene oxide gas (20% ethylene oxide - 80% carbon dioxide) for 24 hours at a temperature of 128°F and a gauge pressure of 30 pounds per square inch.

After removal from the gas sterilizer, the suture envelopes were sealed aseptically and then overwrapped with a strippable outer plastic envelope. The envelopes were boxed in cartons and then replaced in the sterilizer and exposed once again to ethylene oxide gas under the conditions described above in order to sterilize the outside of the inner and inside of the outer envelope.

- (b) In this experiment the black hooded female rat of the Long-Evans strain was used. The animals weighed between 125 and 140 grams at the time of suture implantation. All animals were maintained on a standard laboratory diet made by Rockland Farms and distributed by Teklad, Inc. of Monmouth, Illinois. The guaranteed analysis indicated the following: Crude protein, 24%; Crude fat, 4%; Crude fiber, 6%. Water was available to the animals ad libitum and all animals were housed separately. Sufficient numbers of animals were operated to insure that 3 rats would be available 3 and 6 months after implantation, 5 rats 12 months after implantation and 10 rats 24 months after implantation.
- (c) The animals were anesthetized with inhalation ether. The ventral abdominal surface was shaved free of hair and a solution of 1:1000 Zephiran was applied. One strand of the blue pigmented linear polyethylene suture was embedded into the abdominal wall at approximately right angles to the anterior-posterior body axis. A segment of natural linear polyethylene suture was embedded about 1 - 1-1/2 inches posteriorly to the first implantation. The embedded sutures were approximately 1-1/2 inches long. The sutures were cut and the ends maneuvered into the puncture defects made by the suture needle. Tincture of Merthiolate was applied to the operative site and the animals were returned to their cages.

- (d) Three animals were sacrificed at 3 and at 6 months, 5 were sacrificed at 12 months and 10 animals were sacrificed at 24 months post-implantation. At sacrifice, the abdomen was visualized and en bloc resections of each suture implantation were obtained. These were prepared for histopathological examination by subjecting the tissues to dehydration procedures which utilized increasing concentrations of ethanol. The blocks were cleared in xylene and placed in paraffin. Paraffin blocks were sectioned at 7 microns. Two slides of each block were prepared. Each slide contained between 7 and 10 sections. One slide was stained with eosin and hemotoxylin and the other with Mallory's trichrome stain.
 - (e) The extent of the tissue reactions was graded by a method in use in this laboratory for over 4 years (references (a) and (b), Section 5 of this Subpart). Table I in Section 6, Appendix, of this Subpart indicates the quantification of the grading system. Generally, grades ranging from - to +++ were assigned to increasing proliferations of particulate cells and tissues invading the embedded suture and suture area. Details of the proliferated cell types and tissues will be found in the several tables under Section 6. Photomicrographs of tissue sections were also obtained after 12 months and 24 months and will also be found in Section 6.
3. Observations made after sacrifice of animals and examination of tissue are given below. Tables II and III show details of cellularity of the reactions to embedded blue and natural linear polyethylene after 3 and 6 month embedments. Table IV shows the pattern of reactions to the embedded sutures after 12 month embedments. Table V shows the cellularity of reaction to natural linear polyethylene after 2 year embedments; Table VI shows the cellularity of reaction to blue pigmented linear polyethylene after 2 year embedments.
- (a) An examination of the data shows that there is a consistent, marked similarity of the reactions from 3 months to 2 years. Aside from a slight increase in neovascularity and the appearance of occasional macrophage cells the reactions exhibit no significant difference from 3 months to 2 years.
- The data show that there was no distinctive difference in pattern of cellularity from 3 months to 2 years between blue pigmented and natural linear polyethylene. There was no variation with respect to capsule thickness, numbers of fibroblasts or neovascularity. In none of these sections was there evidence of chronic inflammation.
- The major tissue component of the reaction to embedded linear polyethylene sutures was a moderately thin, dense collagenous capsule which delineated the suture material. Occasional fibroblasts were observed in the capsule periphery. There was no lymphocytic and little macrophagic infiltration of the embedment area. Foreign body giant cells were absent.
- (b) The reactions to embedded suture materials are not the same from animal to animal. The reactions can, and do, vary within a range of responses. Assuming that there are no uncontrollable contaminants on the suture, i.e. bacteria, these variations can be large or small depending on several conditions. For example, the physical configuration of the suture material can contribute to the overall cellular pattern and range of reactions. Thus, suture materials, braided or twisted from smaller fibrils to form

a larger strand, can elicit greater reaction patterns and a wider variation of reaction from strand to strand and animal to animal than does the reaction pattern resulting from the embedment of a monofilament type strand of the same diameter. Katz and Evans (reference a.) showed that silk sutures of the same original size as linear polyethylene sutures elicit a reaction pattern 4 to 6 times as great as polyethylene. They concluded that this comes about as a result of the invasion of the fibrillar matrix of the suture with a resultant increase on reaction diameter.

The type of material from which the suture is made contributes to the pattern of reaction. Thus, variations of reactions and the reaction itself are seen to be larger if, for example, the material is absorbable than if the suture is nonabsorbable over the same period of implantation. Patterson et al (reference b.) showed distinctive variations of reaction to catgut and silk embedded into the cornea of the rabbit.

The tables show that the variations of the reaction patterns between blue and natural linear polyethylene are quite small. Similar results have been reported in the literature (reference a. and c.). This pattern is most readily seen from the photomicrographs, Figures 1 and 2. Here are illustrated the maximum cellular response to embedded blue and natural linear polyethylene after 1 and 2 years, and the minimum cellular response after 1 and 2 years. It can be seen that the range of responses is very small and that there appears to be no difference in cellular patterns between blue pigmented and natural linear polyethylene sutures.

- (c) Spontaneous tumor development occurred in 2 animals out of the 10 sacrificed at the 2 year interval. No tumors were encountered in the 3, 6 or 12 month animals. Dr. William E. Ribelin, pathologist associated with the Environmental Health Laboratory of the American Cyanamid Company, Princeton, New Jersey, reviewed the 2 year embedments and characterized the tumors encountered. He reported that both blue and natural linear polyethylene sutures elicit a minimal response consisting of thin, compressed, collagenous capsules, separated by a slightly thicker collagenous plaque separating the suture site from either the epidermal surface or the deeper lying panniculus carnosus, depending on which was closer. Dr. Ribelin identified the tumors as a mammary fibro-adenoma from Rat E (M5/1-2/24E), and an adenocarcinoma of the uterus and a mammary adenoma from Rat I (M/5/1-2/24I). Dr. Ribelin stated that none of the tumors were suture related (reference d.).

4. Based on the results which have been presented the following conclusions have been made.

- (a) Monofilament linear polyethylene sutures cause minimal tissue changes after embedment in rats from 3-24 months and as such are safe for use as a suture material in humans.
- (b) Monofilament linear polyethylene sutures colored with pigment F5272 elicit the same pattern of tissue responses as does the nonpigmented suture after embedment in rats from 3-24 months. The pigment therefore is safe for use as a color additive for linear polyethylene suture material.
- (c) Blue pigmented and nonpigmented linear polyethylene sutures show neither toxigenic nor tumorigenic properties after 2 year embedments in rats.

5. The references cited in Subsections 1 to 3 of this Subpart D are as follows:

- (a) Katz, A. R. and Evans, H. D., Jr., M.D. Linear Polyethylene Sutures - An Evaluation of Tissue Reaction. American Journal of Surgery, 103(2): 208-216, February 1962.
- (b) Patterson, H. C., M.D., Katz, A. R. and Evans, H. D., Jr., M.D. Identification of Eye Sutures by Means of Multiple Colors. American Journal of Ophthalmology, 54(6):1033-1055, December 1962.
- (c) Phelan, J. T. Linear Polyethylene, A New Suture Material for Arterial Anastomoses. Surgery, 45(4):674-680, April 1959.
- (d) Ribelin, W. C. Personal communication.

6. Appendix.

Tables I through VI and Figures 1 and 2 follow.

HISTOPATHOLOGIC EVALUATION OF TISSUE REACTION TO EMBEDDED SUTURE MATERIAL

Criterion	Magnification(X)	+	1 Plus	2 Plus	3 Plus	4 Plus
Edema; serous exudate	100	Slight edema of perisuture tissues.	Mod. edema, some exudate in perisuture space.	Marked edema, marked exudate in perisuture space.	...	...
Polymorpho-nuclears(PMN)	440	Few PMN	Some PMN	Mod. leuco-cytosis.	Frank abscess	...
Phage, macro and lymphs	440	Few mono-nuclears.	Some mono-nuclears.	Mod. mono-nuclear infil-tration.	Marked mono-nuclear infil-tration.	...
Foreign body giant cells (FBGC)	440	None - 1 per field.	2-3 per field.	More than 3 per field.	...	...
Fibroblasts	440	Few.	Some in peri-suture area.	Some invasion of suture, suture sur-rounded, some infiltration at lateral borders of suture.	Fibroplasia and extension of invasion beyond 1X radius of suture.	...
Fibrotic capsule	100	Cap. 1-2 cells thick.	3-4 cells thick.	Cap. less than 1/2 suture radius.	Cap. greater than 1/2 suture radius.	...
Intrasuture organization (fibrilar sutures only)	100	...	A few fibro-blasts, scar in matrix.	Mod. invasion of suture and distinctive cords of scar.	Many scar cords with small pockets of fibrils in-tact and unin-vaded.	All suture fi-brils surround-ed and separ-ated by scar, vessels, fibro-blasts.
Neovascularity	440	A few cap-ilaries in perisuture tissues.	Mod. vascular-ity, invasion of suture boundary.	Vascularity sur-rounding suture, invasion of suture matrix.		

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TABLE II

Series M/5(109) - Microscopic Examination

Blue and Natural Linear Polyethylene 000 - 3 Month Embedment in Rats

November 1961

Animal No.	Edema	PMN Leuco.	Plaques		Fibro- blasts	Fibrous Capsule	Giant Cells	Intra-Suture Organization*	Neo-Vascu- larization
			Lymphs	Macro.					
Blue {	M/5/1/3m A	-	-	-	+	+	-	-	+
	M/5/1/3m B	-	-	-	-	+	-	-	+
	M/5/1/3m C	-	-	-	-	+	-	-	+
Natural {	M/5/2/3m A	-	-	-	+	+	-	-	+
	M/5/2/3m B	-	-	-	+	+	-	-	+
	M/5/2/3m C	-	-	-	-	+	-	-	-

Key:

- = Negative
- + = Trace
- + = Slight
- ++ = Moderate
- +++ = Marked
- ++++ = Complete Organization

*Intra-suture organization:
ingrowth of fibroblasts and/or
blood vessels between individual
fibers of suture materials.

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TABLE III

Series M/5(109) - Microscopic Examination

Blue and Natural Linear Polyethylene, 000 - 6 Month. Embedment in Rats

May 1962

Animal No.	Edema	PMN Leuco.	Lymphs	Phages Macro.	Fibro- blasts	Fibrous Capsule	Giant Cells	Intra-Suture Organization*	Neo-Vascu- larization
Blue { M/5/1/6m A M/5/1/6m B M/5/1/6m C	-	-	-	-	+	++	-	-	+
	-	-	-	-	-	+	+	-	-
	-	-	-	-	-	+	+	-	+
Natural { M/5/2/6m A M/5/2/6m B M/5/3/6m C	-	-	-	-	-	+	-	-	+
	-	-	-	-	++	++	-	-	+
	-	-	-	-	-	+	-	-	+

Key:

- = Negative
+ = Trace
+ = Slight
++ = Moderate
+++ = Marked
++++ = Complete Organization

*Intra-suture organization:
ingrowth of fibroblasts and/or
blood vessels between individual
fibers of suture materials.

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TABLE IV

Series M/5(109) - Microscopic Examination

Blue and Natural Linear Polyethylene, 000 - 1 Year Embedment in Rats

September 1962

Animal No.	Edema	PMN Leuco.	Lymphs	Phages Macro.	Fibro- blasts	Fibrous Capsule	Giant Cells	Intra-Suture Organization*	Neo-Vascu- larization
Blue	M/5/1/12m A	-	-	-	-	+	-	-	+
	M/5/1/12m B	-	-	-	-	+	-	-	-
	M/5/1/12m C	-	-	-	-	+	-	-	-
	M/5/1/12m D	-	-	+	+	+	-	-	+
	M/5/1/12m E	-	-	-	++	+++	-	-	++
Natural	M/5/2/12m A	-	-	-	-	+	-	-	-
	M/5/2/12m B	-	-	-	-	+	-	-	-
	M/5/2/12m C	-	-	-	-	+	-	-	+
	M/5/2/12m D	-	-	+	+	+	-	-	-
	M/5/2/12m E	-	-	-	-	+	-	-	+

Key:

-	=	Negative
+	=	Trace
+	=	Slight
++	=	Moderate
+++	=	Marked
+++	=	Complete Organization

*Intra-suture organization: ingrowth of fibroblasts and/or blood vessels between individual fibers of suture materials.

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TABLE V
Series M/5(109) - Microscopic Examination
Natural Linear Polyethylene, 000 - 24 Month Embedment in Rats
November 1963

Animal No.	Edema	PMN Leuco.	Lymphs	Phages Macro.	Fibro- blasts	Fibrous Capsule	Giant Cells	Intra-Suture Organization*	Neo-Vascu- larization
M/5/2/25 A	-	-	-	+	+	+	-	-	+
" B	-	-	-	-	+	+	-	-	+
" C	-	-	-	+	+	+	-	-	+
" D	-	-	-	+	+	++	-	-	+
" E	-	-	-	+	+	+	-	-	+
" G	-	-	-	+	+	+	-	-	+
" I	-	-	-	+	+	+	-	-	+
" J	-	-	-	-	+	+	-	-	+
" K	-	-	-	+	+	+	-	-	+
" N	-	-	-	-	-	+	-	-	+

Key:

- = Negative
+ = Trace
+ = Slight
++ = Moderate
+++ = Marked
++++ = Complete Organization

*Intra-suture organization: ingrowth of fibroblasts and/or blood vessels between individual fibers of suture materials.

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Subpart E

1. Probable Consumption and Exposure of Pigment Plus Suture Material in the Body.

The blue linear polyethylene is used as a skin suture and is usually removed from the wound area after 7 days. The maximum length of suture material in contact with the body internally and externally would be about 10 inches if a continuous stitch is used. Since the fiber is hydrophobic, there is probably no leaching of the pigment into the surrounding cells. The following test was used to determine if there is any leaching of the pigment off the fiber.

Three 60 foot samples of size 000 blue linear polyethylene were immersed in 100 ml. of the following solutions: Normal Saline, Weak Acid (pH 5.2) and Weak Base (pH 7.5). These solutions with their 60 foot suture coils were stored in an incubator at 37°C for 7 days. At the end of this period, the solutions were evaporated to 20 ml. and qualitatively spot tested for chromium, cobalt and aluminum cations. These tests were obtained from Feigl Spot Tests Vol. 1, and are given below.

Chromium

"Procedure. A drop of the neutral or weakly acid test solution is treated, on a spot plate, with one or two drops of sodium hypobromite solution. After about a minute, a drop of concentrated sulfuric acid and one or two drops of sulfosalicylic acid are introduced and then a drop of alcoholic diphenylcarbazide solution. A violet color appears; its intensity depends on the quantity of chromium present.

Limit of Identification: 0.25 μ chromium

Dilution Limit: 1:200,000. The above identification limit holds also in the presence of 1000 times the quantity of manganese, nickel or cobalt.

- Reagents:
- 1) Freshly prepared alkaline hypobromite solution (5 ml. bromine water plus 2 ml. 5 N sodium or potassium hydroxide, plus 2 g. potassium bromide)
 - 2) Concentrated sulfuric acid
 - 3) 20% aqueous solution of sulfosalicylic acid
 - 4) Saturated solution of diphenylcarbazide in alcohol"

Results on the test solutions were negative for the 100 ml. and 20 ml. concentrates of all the leach solutions.

Aluminum

"Procedure. A small drop of the neutral or weakly acid test solution is placed on potassium ferrocyanide paper. The other ions are "fixed" in the paper as insoluble ferrocyanides. The aluminum diffuses along with the water beyond the precipitate. Most of the aluminum can be washed into the outer zone by the addition of another drop of water to the middle of the fleck.

A drop of alizarin is added; the paper is held over ammonia and dried. A red ring of alizarin-aluminum lake is formed around the ferrocyanide precipitate. In order to make the product visible, it is advisable, after the reaction is complete, to place the paper, for about 2 minutes, in hot water. Some of the metal ferrocyanides are washed off and the aluminum lake becomes more visible.

The limits of identification for aluminum in the presence of varying amounts of the other metals, according to this method, are:

4.0 y Al	in the presence of	300 y Fe	
3.0 y Al	"	"	300 y Fe + 750 y Cr
1.4 y Al	"	"	3912 y Mn
0.6 y Al	"	"	60 y Fe + 372 y Mn
0.6 y Al	"	"	30 y Fe + 180 y Zn
0.1 y Al	"	"	30 y Zn + 20 y Mn
0.5 y Al	"	"	100 y U
0.6 y Al	"	"	30 y Fe + 72 y Co"

Results on the test solutions were negative for the 100 ml. and 20 ml. concentrates of all the leach solutions.

Cobalt

"Procedure. A drop of the test solution is placed on filter paper, held over ammonia, and then spotted with a drop of the reagent solution. In the presence of cobalt, a brown fleck or ring is formed.

A large excess of ammonium salts reduces the sensitivity.

Limit of Identification: 0.03 y cobalt

Dilution Limit: 1:1,660,000

Reagents: 1) Ammonia
2) 1% alcohol solution of rubeanic acid"

Results on the test solutions were positive for the 100 ml. and the 20 ml. concentrates of all the leach solutions but were no greater than the demineralized water blanks. The amount of cobalt detected was of the order of 0.03 ppm and it is believed that all of it was supplied by the water and not by the suture material.

Subpart F

1. Proposed Restrictions and Tolerances on the Use of the Pigment.
There are no restrictions or tolerances proposed for pigment F5272.

Subpart G

1. Exemption from Batch Certification.
Davis & Geck requests an exemption from certification for the chromium, cobalt and aluminum oxides (Pigment F5272) used to color a linear polyethylene suture material blue for the following reasons.

(a) The animal experimentation work and data, in Subpart D, clearly establish that this pigment (F5272) when used to color a linear polyethylene surgical suture is noninjurious to health if applied by standard surgical techniques.

- (b) The coloring pigment F5272 is firmly embedded in an inert matrix and does not leach out of the fiber.
- (c) The oxide components of the pigment are insoluble in aqueous solution of near neutral pH and these oxides are unreactive, stable and in themselves nontoxic.
- (d) Each lot of blue linear polyethylene is assayed by spectrographic and chemical methods to assure that this suture material is the same as the suture material used for the animal tissue reaction studies in Subpart D.

FIGURE 1

Monofilament Linear Polyethylene, Size 000, 12 Month Embedments in Rats



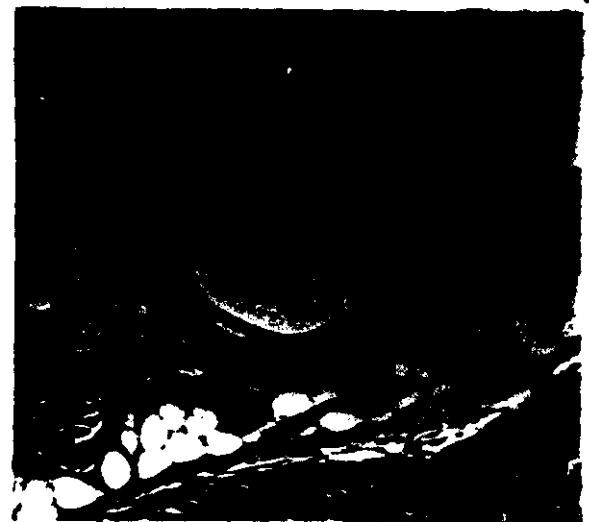
A
Most reaction, natural polyethylene



B
Least reactive, natural polyethylene



C
Most reaction, blue polyethylene



D
Least reactive, blue polyethylene

H&E AFX. 120X

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000

FIGURE 2

Monofilament Linear Polyethylene, Size 000, 24 Month Embedment in Rats



A
Most reactive, natural polyethylene



B
Least reactive, natural polyethylene



C
Most reactive, blue polyethylene



D
Least reactive, blue polyethylene

MALLORY'S TRICHROME AFX. 120X

.133

AF 17-081

AF 14-731

Incorrect AF

February 20, 1964

Boyle & Gask
Division of American
Cyanamid Company
Hartford, Connecticut

Attention: H. B. Dunn Jr., H.B.

Continued:

We acknowledge receipt on February 3, 1964, of your petition for a regulation to list Chromium, Cobalt, and Aluminum Oxide Pigment for use in or on surgical sutures made of linear polyethylene. We have already acknowledged receipt of your check for \$10,400, from which \$2400 is to be taken as the fee for the filing of this petition. This petition has been designated Color Additive Petition No. 12.

We have completed our preliminary review of this petition and have concluded that it is incomplete in a number of respects and, therefore, may not be filed at this time.

The areas in which we regard the petition as incomplete are as follows:

1. No information is presented regarding the facilities and controls employed in the manufacture of the color additive. This information should show that the composition of the color additive is reproducible. The Farnco Corporation may furnish this information directly to us.

2. No specific analytical data has been presented which shows the color additive content of the sutures tested pharmacologically.

3. It is not clear to us just what the composition of the pigment is. There is an apparent discrepancy between the spectrographic analysis and the chemical analysis by you. We are particularly confused by the amount of Soret reported in the spectrographic analysis. Neither of these analyses agree with the chemical composition as furnished by the Farnco Corporation.

4. The petition gives conflicting data about the amount of pigment in the suture, (the "f" value in spectrographic analysis and page 7 of the petition) and no data has been submitted showing reproducibility of the suture coloring procedure.

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3. In the method for the quantitative analysis of the pigment in the culture, the pigment is added and passed through a 70-mesh sieve. What is the purpose of the sieve? Is the entire ash passed through the sieve?

4. Apparently, the pharmacological investigation was made using cultures containing approximately 11 pigment. What is the basis for the requested 11 limit?

We will hold the petition pending advice from you. Our scientific divisions will be glad to discuss further with you the information requested in this letter.

Sincerely yours,

D. J. Miller
Assistant to the Director
Division of Color Certification
and Evaluation

cc: Dr. David Hudson
Technical Director
David & Gask

MMH MCCM MCE CAP12

DJMiller:cmh 2/20/64
ED Sign DJMiller

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CAP #12, Aluminum, Cobalt, Chromium Oxide
CAP #13, Pyrogallol and Iron
CAP #14, D&C Blue No. 9

May 5, 1964

#12

MEMORANDUM OF CONFERENCE

Participants: Walter M. Thomas - American Cyanamid Co.
David Kaufman - Davis & Geck

Dr. K. A. Freeman - DCCE
Mr. W. B. Link - DCCE
Mr. D. J. Miller - DCCE

Dr. Kaufman and Mr. Thomas requested the conference in order to discuss deficiencies in Color Additive Petition No. 12 for Aluminum, Cobalt and Chromium Oxide, and Color Additive Petition No. 13 for Pyrogallol and Iron, and certain requested information in connection with Color Additive Petition No. 14 for D&C Blue No. 9.

We had asked Davis & Geck to furnish information about the amount of D&C Blue No. 9 in both the sutures tested pharmacologically and batches of sutures prepared thereafter. Dr. Kaufman said that they had prepared only the one batch that was tested pharmacologically and that, therefore, had no way of comparing various batches. We had also requested samples of sutures dyed with the D&C Blue No. 9, as well as undyed samples of silk and cotton sutures. Dr. Kaufman said that some of the silk sutures were not yet in commercial production but they were being prepared and would be submitted as soon as available.

We had asked Davis & Geck to furnish additional information about Chromium, Cobalt and Aluminum Oxide pigment used in linear polyethylene sutures. Dr. Kaufman replied to the specific points raised in our February 20, 1964 letter as follows. (The paragraph numbers correspond to those in our 2/20/64 letter.)

1. Davis & Geck will ask the Ferro Corporation to send in additional information about manufacturing operations. (Dr. Kaufman asked us to notify the Davis & Geck Company if and when Ferro Corporation submits this additional information.)

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May 5, 1964

2. The material tested pharmacologically had the same analysis as that which was submitted in the petition.
3. Davis & Geck will check with the Ferro Corporation regarding the discrepancies in the analytical values as determined by Ferro Corporation and Davis & Geck.
4. Additional information will be submitted which will clarify the "ash" content and the amount of pigment in the suture.
5. The purpose of the sieve is to break up lumps, and the material is brushed with the sieve until all passes through.
6. Dr. Kaufman said they had no real basis for requesting a 2% limit of pigment in sutures but that they wanted to be on the safe side in the event they exceeded the 1% they aimed for. Dr. Kaufman pointed out that they expected to use very few lots of the Chromium, Cobalt and Aluminum Oxide pigment. He said several hundred pounds would last approximately ten years. He said they had made some additional analyses, particularly with respect to boron and will furnish these analyses.

By letter of February 25, 1964, we had asked Davis & Geck to furnish additional information about Pyrogallol and Iron Salt as color additives on absorbable surgical sutures. Dr. Kaufman's comments on the correspondingly numbered points in our letter are as follows:

1. Davis & Geck are working on a qualitative identification test which they hope will have some value from a quantitative standpoint. This information will be submitted when it is completed.
2. They will submit additional information by weighing batches of sutures before and after passing through the dye bath.
3. They will submit information about in vitro fastness of dyed sutures.

We had asked Davis & Geck about the possible conflict with the USP XVI, since that compendium did not authorize the coloring of absorbable sutures. Dr. Kaufman said that he had been in touch with Dr. Lloyd Miller of the USP revision committee and that there is expected to be a revision of the monograph on absorbable sutures which will permit the use of coloring agents.

D. J. Miller

cc: DTE, DCC~~E~~ (Mr. Link),
OC (Mr. Neprud)
CAP #12, CAP #13, CAP #14

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CAP #14 - D&C Blue No. 9. Dr. Kaufman said that Davis & Geck had not manufactured all of the various size sutures and therefore could not give us all the samples we had requested. I asked Dr. Kaufman to send us samples of whatever sutures colored with D&C Blue No. 9 were available and we would let him know if we needed more.

Dr. Kaufman said that he noted that Ethicon had submitted a petition for Logwood - Fustic, as a color for sutures and inquired whether Davis & Geck would have to do so also. I said I did not think so at the moment. I pointed out that it might be necessary to include in a regulation a description of the dyeing process and if the one used by Davis & Geck was not essentially the same, then their sutures would not qualify under the regulation. I said if it turned out that the dyeing method used by Davis & Geck differed materially from the one in the regulation, Davis & Geck would have to request an amendment to the regulation. I suggested to Dr. Kaufman that he informally submit Davis & Geck's dyeing procedure to us.

Dr. Kaufman said that the firm had just about completed the pharmacological work on the use of D&C Blue No. 6 in dacron sutures, and that he hoped they would be filing a petition for it in the not too distant future.

Dr. Kaufman asked about the status of D&C Blue No. 9 after July 1, 1965, the present closing date. I said that since the petition was filed we would consider postponing the closing date on our own initiative, but I thought it advisable, nevertheless, that he make a formal request for postponement of the closing date.

D. J. Miller

DJMiller:vs 3/29/65
RD Sgd DJMiller

cc: CAP #12 ✓
CAP #13
CAP #14
DTE
BSSK(Data Processing)
CCE(link)
CCE(Miller)

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August 18, 1965

Davis & Geck
Danbury, Conn
AF 17-081

Mr. Aladar Baryan
Director of Color R & D
Ferro Corporation
4150 East 56th Street
Cleveland 5, Ohio

Dear Mr. Baryan:

We acknowledge receipt of your letter of May 14, 1965, in which you submit additional information about the composition of your blue-green pigment F-5272 which is being used to color polyethylene sutures manufactured by Davis & Geck, Division of American Cyanamid Company.

While the additional information has answered most of our questions, we still are somewhat uncertain as to the actual lead and arsenic content of the pigment. Our general specifications for color additives require that color additives used for ingested drugs contain not more than 10 ppm of lead and 1 ppm of arsenic, unless other limits are specifically stated in an individual regulation. (We would expect colors used in sutures to meet general specifications for ingested drugs.) In the case of a water-insoluble color additive, lead and arsenic are determined in a solution obtained by boiling 10 grams of the color additive for 15 minutes in 50 milliliters of half normal hydrochloric acid.

Can you furnish us with the lead and arsenic content of typical batches of pigment F-5272 using the above procedure?

Sincerely yours,

D. J. Miller
Assistant to the Director
Division of Color Certification
and Evaluation

cc: Dr. David Kaufman
Davis & Geck
Division of American
Cyanamid Company
Danbury, Connecticut

cc: BYE, CCE(Link), CAP#12
DJMiller:amb 8/18/65 ED Sgd DJMiller

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AF 17-081

November 9, 1965

Davis & Geck
Division of
American Cyanamid
Danbury, Connecticut 06813

Gentlemen:

We are filing your Color Additive Petition No. 12 to list chromium, cobalt, aluminum oxide pigment as a safe color additive for linear polyethylene surgical sutures, on November 9, 1965.

We are sure you understand that filing of this petition does not necessarily mean that we are completely satisfied that the data submitted as of this date will support a regulation listing this color additive as safe for its proposed use.

If more data is needed, we will make specific requests at a later date.

Sincerely yours,

Kenneth A. Freeman, Director
Division of Color Certification and Evaluation

cc: JTB, CCE(Link), CAP#12

amb 11/9/65

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FEDERAL REGISTER, VOL. 30, NO. 227—WEDNESDAY, NOVEMBER 24, 1965

**DEPARTMENT OF HEALTH, EDU-
CATION, AND WELFARE**

Food and Drug Administration

DAVIS & GECK

**Notice of Filing of Petition Regarding
Color Additives**

Pursuant to the provisions of the Fed-
eral Food, Drug, and Cosmetic Act (see
706(d), 74 Stat. 403; 21 U.S.C. 376(d)),

notice is given that a petition (CAP 12)
has been filed by Davis & Geck, Division
of American Cyanamid Co., Danbury,
Conn., 06813, proposing the issuance of
a regulation to provide for the safe use
and exemption from certification of
chromium-cobalt-aluminum oxide pig-
ment as a color for linear-polyethylene
surgical sutures.

Dated: November 18, 1965.

MALCOLM R. STEPHENS,
*Assistant Commissioner
for Regulations.*

[F.R. Doc. 65-12633; Filed, Nov. 23, 1965;
8:50 a.m.]

Page 14606
FR

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(Published in the Federal Register:
November 24, 1965; 30 F.R. 14606)

DAVIS & GECK

**Notice of Filing of Petition Regarding
Color Additives**

Pursuant to the provisions of the Federal Food, Drug, and Cosmetic Act (sec. 706(d), 74 Stat. 403; 21 U.S.C. 376(d)), notice is given that a petition (CAP 12) has been filed by Davis & Geck, Division of American Cyanamid Co., Danbury, Conn. 06813, proposing the issuance of a regulation to provide for the safe use and exemption from certification of chromium-cobalt-aluminum oxide pigment as a color for linear-polyethylene surgical sutures.

Dated: November 18, 1965.

MALCOLM R. STEPHENS,
*Assistant Commissioner
for Regulations.*

000088

AF 17-081
Davis & Geck Division of
American Cyanamid
Danbury, Conn.

January 26, 1966

Mr. Aladar Burgyan
Color Division
Ferro Corporation
4150 East 56th Street
Cleveland, Ohio 44105

Dear Mr. Burgyan:

We are presently preparing a regulation listing chromium, cobalt, aluminum oxide as a color additive for coloring linear polyethylene surgical sutures. The Davis & Geck Division of American Cyanamid has petitioned for this use and as you know, are using your pigment F-5272 as the color.

We are considering incorporating the following "Identity" and "specifications" paragraphs:

"(a) Identity. The color additive chromium, cobalt, aluminum oxide is a blue pigment obtained by calcining a mixture of chromium oxide, cobalt carbonate, and aluminum oxide. It may contain small amounts (less than 1% each) of barium, boron, silicon, and nickel oxides.

"(b) Specifications. Chromium, cobalt, aluminum oxide shall conform to the following specifications:

Chromium, calculated as Cr_2O_3 , 34-37 percent.
Cobalt calculated as CoO , 30-33 percent.
Aluminum calculated as Al_2O_3 , 28-31 percent.
Lead (as Pb), not more than 10 parts per million.
Arsenic (as As), not more than 1 part per million.
Total oxides of aluminum, chromium, and cobalt,
not less than 97 percent.
Lead and arsenic shall be determined in the solution
obtained by boiling 10 grams of the chromium, cobalt,
aluminum oxide for 15 minutes in 50 milliliters of
0.5% hydrochloric acid."

We are not unmindful that in your letters of February 4, 1963 and May 14, 1965 you have specifically requested that we maintain the confidentiality of the information furnished in your letters. We would like to comply with your request to the extent possible. However, under the law the

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(Ferro Corporation)

-2-

identity of a color additive and, where necessary, its specifications must be described in the regulation listing the color additive. The "identity" and "specifications" paragraphs above are the minimum that we feel will adequately describe your P-5272.

Frankly, we do not think these paragraphs are particularly revealing of confidential information since any competent laboratory could make a reasonably accurate elemental analysis of the pigment. Before issuing a regulation, however, we would like your comments on the proposed paragraphs.

Sincerely yours,

David J. Miller, Deputy Director
Division of Color Certification & Evaluation

cc: TE, CCE(Link), CAP#12

DJMiller:smb 1/26/66

RD Sgd DJMiller

064

Gold Standard

Cable Tension American

American Silk Sutures, Inc.

Roslyn Heights, New York, U.S.A.

12
June 14, 1965
Subman

Mr. D.J. Miller
Department of Health, Education and Welfare
Food and Drug Administration
501 First Street, S.E. Room 240
Washington, D.C.

Dear Mr. Miller:

May I thank you again for the courtesy that you extended to me on my visit to you on the 8th of June.

I am having compiled, and will forward to you, the complete processes which we utilize in apply the Logwood dye and the Blue D and C #9 as you suggested. I will also supply you with all of the information on our testing at the same time.

Enclosed for your information is a complete list of the dye stuff discussed at the U.S. Pharmacopolia Official on Wednesday, August 19, 1964 that were being considered by all of the manufacturers for use in sutures. From this, you can ascertain that the list is comparatively limited and utilized by all manufacturers. I trust that this will be of some assistance to you.

In checking through my notes, I also noted that at the time also included in the discussion on the pure pigments we included the carbon impregnation and the impregnation with copper phthalocyanine as well as the chromium cobalt aluminum mixture for polyethylene.

Again may I thank you for your courtesy and cooperation.

Sincerely,

AMERICAN SILK SUTURES, INC.

Win Hirsch
Win Hirsch
President

WH:md
enc.

mal amount of each dye required to produce a tattoo in human skin would be expensive and time consuming. Accordingly, the group felt that the problem of defining the maximal permissible limit of uncombined dye for each dye used in the suture industry could be handled by (1) listing each dye presently used in suture manufacture and (2) collaborating among manufacturers to arrive at practical upper limits for uncombined dye for each type of dye in use. A listing of dyes being used in the industry shows the following:

Pyroallol - Iron	} Group I
D and C Red #10	
FD and C Blue #2	
D and C Blue #9	
D and C Violet #1	
Logwood (Alcaline #7)	} Group II
and Fustic AA))	
D and C Green #5	
D and C Green #6	
D and C Blue #6	

Copper phthalocyanine, chromium, cobalt, and aluminum oxides were also listed, but it was stated that standards for various concentrations of these substances could not be made.

Color Division
CERAMIC • GLASS • PLASTIC

FERRO CORPORATION

COLOR DIVISION HEADQUARTERS
4150 EAST 58th STREET
CLEVELAND 5, OHIO

September 28, 1965

Mr. David T. Miller
Assistant to the Director
Division of Color Certification
and Evaluation
Food & Drug Administration
Department of Health, Education and Welfare
Washington, D. C. 20204

*File
CAP #12*

Dear Mr. Miller:

Your letter of August 18, 1965, requesting data on lead and arsenic content of our F-5272 turquoise pigment being used to color polyethylene sutures made by Davis and Geck, Division of American Cyanamid Company, has been received.

Our Technical Services Laboratory ran the analysis on three different lots of pigments and found, unexpectedly, lead and arsenic in greater amounts than the specifications mentioned in your letter above call for.

Therefore, we submitted 2 more pigment samples for analysis. This time the pigment was acid-washed, a procedure widely used for quality improvement in the pigment industry, and the lead and arsenic content dropped sufficiently below the specified level.

The acid washed pigments are designated by the capital letter "W" and the enclosed analytical report is self-explanatory.

In view of these findings we now are confident to be able to manufacture F-5272-W which will contain not more than 10 ppm lead and not more than 1 ppm arsenic, and thus to meet the general specifications for color additives used for ingested drugs.

Very truly yours,



Aladar Burgyan
Director of Color R & D

AB:md
Enclosure (1)
cc: Dr. David Kaufman
Davis & Geck
Div. of American Cyanamid Co.
Danbury, Connecticut

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FERRO CORPORATION
4150 East 56th St.
Fairfield 5, Ohio

Laboratory No. 5723 & 5743
Requisition No. _____

REPORT FROM THE
TECHNICAL SERVICES LABORATORY

SAMPLE F 5272 COLORS FOR Pb and As
DATE RECEIVED 8/23/65 DATE REPORTED 9/20/65
REQUESTED BY Burgyan DEPT. 6-31-63 PROJECT _____
FILE REFERENCE RZ 1136-1137, RZ 1141

3 - F 5272 UNTREATED COLORS FOR Pb and As

	<u>Lot #</u>	<u>Pb</u>	<u>As</u>
F-5272	12-043-40	214 ppm	<1.9 >1.5 ppm
"	08-030-00	176	<.08
"	05-069-50	82	1.9

2 - F 5272 ACID WASHED COLORS FOR Pb and As

	<u>Lot #</u>	<u>Pb</u>	<u>As</u>
F-5272 W	05-072-50	6 ppm	nil
"	12-043-40	8	nil

The lead and arsenic were determined in a solution obtained by boiling 10 grams of the color additive for 15 minutes in 50 milliliters of 0.5 N HCl.

The arsenic was determined by the Gutzeit Method and the lead spectrographically.

br
cc: Burgyan (3)
Bozsia
File

000072

REPORTED BY: DJ Salasek

D. J. Salasek

STAMFORD RESEARCH LABORATORIES

RESEARCH SERVICE DEPARTMENT REPORT

TO Mr. A. Glick	DEPT. Davis & Geck	ROOM NO.
FROM General Analytical II	DATE REPORTED 9/20/65	
MATERIAL Blue Pigment	TEST Pb; As	
CHARGE NO. 2086-09	DATE SUBMITTED 6/2/65	
WORK REPORTED BY G. A. Clarke	NOTEBOOK REFERENCE S-7357 - 27	

WORK DONE BY E. Burroughs

<u>Sample Identification</u>	<u>Lead as PPM Pb</u>	<u>Arsenic as PPM As</u>
F 5272 Blue	35	none found

In each case a 10 g. sample was boiled in 0.5N HCl for 15 minutes and the solution was filtered and evaporated to dryness.

Lead was determined by the procedure described in the attached method P 28 c. Estimated limit of sensitivity 1 ppm.

Arsenic was determined by the procedure described in the attached method P 28 d. Estimated limit of sensitivity 0.1 ppm.

G. A. Clarke
G. A. Clarke

emb

STAMFORD RESEARCH LABORATORIES

RESEARCH SERVICE DEPARTMENT REPORT

TO	Mr. A. Glick	DEPT.	Davis & Geck	ROOM NO.
FROM	General Analytical II	DATE REPORTED	9/20/65	
MATERIAL	Pigment	TEST	Pb; As	
CHARGE NO.	2086-09	DATE SUBMITTED	6/2/65	
WORK REPORTED BY	G. A. Clarke	NOTEBOOK REFERENCE	S-7357 - 21-27	

WORK DONE BY E. Burroughs

<u>Sample Identification</u>	<u>Lead as ppm Pb</u>	<u>Arsenic as ppm As</u>
D and C Blue 9 Lot F4762	2.6, 2.3	0.2

Lead was determined by attached procedure P 28 c. Estimated limit of sensitivity 1 ppm.

Arsenic was determined by attached procedure P 28 d. Estimated limit of sensitivity 0.1 ppm.

G. A. Clarke

G. A. Clarke

amb

STAMFORD RESEARCH LABORATORIES

RESEARCH SERVICE DEPARTMENT REPORT

TO	Mr. A. Glick	DEPT.	Davis & Geck	ROOM NO.
FROM	General Analytical II	DATE REPORTED	9/20/65	
MATERIAL	Sutures	TEST	Pb; As	
CHARGE NO.	2086-09	DATE SUBMITTED	6/2/65	
WORK REPORTED BY	G. A. Clarke	NOTEBOOK REFERENCE	S-7357 - 27	

WORK DONE BY E. Burroughs

<u>Sample Identification</u>	<u>Lead as ppm Pb</u>	<u>Arsenic as ppm As</u>
Blue Linear Polyethylene	1	none found

In each case a 10 g. sample was boiled in 0.5N HCl for 15 minutes and the solution was filtered and evaporated to dryness.

Lead was determined by the procedure described in the attached method P 28 c. Estimated limit of sensitivity 1 ppm.

Arsenic was determined by the procedure described in the attached method P 28 d. Estimated limit of sensitivity 0.1 ppm.

G. A. Clarke
G. A. Clarke

amb

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Determination of Lead in Organic Materials

Principle of the Method

The sample is ashed at a low temperature in the presence of sodium carbonate to destroy the organic matter. A slightly basic solution of the residue is prepared, and the lead concentration is determined colorimetrically by a dithizone extraction procedure.

Apparatus

1. Separatory funnels, 125-ml.
2. Spectrophotometer, Beckman Model B or any instrument capable of making measurements at a wave length of 520 mμ, equipped with 1-cm silica cells.

Reagents

1. Sodium carbonate, anhydrous.
2. Carbon tetrachloride, reagent grade.
3. Dithizone solution. A 0.001 to 0.0012% (W/V) solution of diphenylthiocarbazone (Eastman 3092) in carbon tetrachloride.
4. Ammonium hydroxide, concentrated and 8N.
5. Nitric acid, ~ 0.16N.
6. Ammonium citrate solution. Dissolve 5.0 g. of ammonium citrate in 100 ml. of water. Adjust the solution to pH9 with ammonium hydroxide and shake with successive portions of dithizone solution until the extracts remain colorless. Extract excess dithizone from the solution with chloroform.
7. Potassium cyanide solution. Dissolve 10 g. of potassium cyanide in 100 ml. of water. Extract with 0.005% dithizone solution to remove any lead.
8. Hydroxylamine hydrochloride solution. Dissolve 20 g. of hydroxylamine hydrochloride in 100 ml. of water.
9. Ammonia-cyanide-sulfite solution. Mix 7.25 ml. of 8N ammonium hydroxide solution with 30 ml. of 10% potassium cyanide solution and dilute to one liter. Dissolve 1.5 g. of sodium sulfite in the solution.
10. Standard lead solutions.
Solution A, 0.1 mg. Pb/ml. Dissolve 0.160 g. of dried lead nitrate in one liter of 0.16N nitric acid.

Solution B, 1 microgram Pb/ml. Dilute 10 ml. of solution A to one liter with 0.16N nitric acid. Prepare fresh just prior to use.

Preparation of Calibration Curve

Carry 1, 2, 5, 10, 15, and 20 ml. of standard solution B through the following procedure:

Measure the standard into a 125-ml. separatory funnel and add sufficient 0.16N nitric acid to bring the volume to 25 ml. Add 10 ml. of ammonia-cyanide-sulfite solution and exactly 10 ml. of 0.001% dithizone solution. Shake well for one-half minute, allow the phases to separate, and run a portion of the carbon tetrachloride phase through a plug of glass wool into a one-cm. cell. Measure the absorbance at 520 mμ vs. carbon tetrachloride in a reference cell. Carry a blank of 25 ml. of 0.16N nitric acid through the same procedure. Correct the observed readings for the blank and plot the corrected reading vs. micrograms Pb/10 ml.

Preparation of Sample

Weigh a suitable quantity of sample (containing 1 to 20 micrograms of lead) into a tared silica or platinum dish and mix intimately with one-fifth its weight of anhydrous sodium carbonate. Place in a cool muffle furnace (100° - 500°C), raise the temperature to about 420°C and leave overnight. Cool, and leach with about 10 ml. of 1:1 hydrochloric acid, heating to near the boiling point for 5-10 minutes. Filter off any insoluble material, washing with a small volume of hot 1:1 hydrochloric acid. Reserve the filtrate and washings; discard the residue.

Procedure

Add 10 ml. of ammonium citrate solution, 1 ml. of hydroxylamine hydrochloride solution, and a few drops of thymol blue indicator to the solution reserved above. Make the solution slightly basic with ammonium hydroxide, and add 5 ml. of potassium cyanide solution. Adjust the pH to 9 - 9.5 (green-blue to blue color) by dropwise addition of ammonium hydroxide. Transfer the solution to a separatory funnel, add 5 ml. of dithizone solution and shake for one-half minute. Allow the phases to separate and drain the carbon tetrachloride phase into a second separatory funnel. Repeat the extraction with 5-ml. portions of dithizone until the extract is colorless. Combine the extracts and wash them by shaking with 10 ml. of water containing a drop of 1:1 ammonium hydroxide. Draw off the carbon tetrachloride phase into a third separatory funnel. Shake the aqueous phase with 1 to 2 ml. of carbon tetrachloride and add this extract to the contents of the third separatory funnel.

Extract the lead from the carbon tetrachloride solution by shaking with two successive 5-ml. portions of 0.16N nitric acid for one-half minute. Combine the acid extracts in a separatory funnel, wash the carbon tetrachloride phase with two ml. of water and add this washing to the acid extracts. Add 10.0 ml. of ammonia-cyanide-sulfite solution and exactly 10 ml. of 0.001% dithizone solution and shake for one-half minute. Allow the phases to separate and run a portion of the carbon tetrachloride phase through a plug of glass wool into a 1-cm. cell. Measure the absorbance at 520 mμ vs. carbon tetrachloride in a reference cell. Avoid exposure to strong sunlight. Carry a blank of 25 ml. of 0.16N nitric acid through the determination and correct the observed readings for any blank. Determine micrograms Pb/10 ml. by reference to the calibration curve.

$$\text{ppm lead} = \frac{\text{micrograms Pb/10 ml.}}{\text{g. of sample}}$$

General Analytical Group II
August, 1965

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Determination of Arsenic in Organic Materials

Principle of the Method

The sample is digested under reflux with sulfuric and nitric acids to destroy the bulk of the organic matter, and then treated with perchloric acid to remove any remaining traces of organic material. The dissolved arsenic is subsequently converted to arsine and determined colorimetrically with silver diethyldithiocarbamate in pyridine. The only metal likely to interfere is antimony.

Apparatus

1. Digestion Apparatus

- a. Boiling flask, 300-ml., center neck $\frac{1}{2}$ 24/40, side neck $\frac{1}{2}$ 24/40 (Kontes K 60500).
- b. Funnel, separatory, 125-ml. $\frac{1}{2}$ 24/40 joints (Kontes 63400).
- c. Funnel, filling, 60-ml. $\frac{1}{2}$ 24/40 joint (Kontes 63125).
- d. Condenser, straight, 200 mm $\frac{1}{2}$ 24/40 joints (Kontes K 44650).
- e. Electric heater, any convenient type with variable temperature control.

Assemble the above components as follows: Place the boiling flask on the electric heater. Insert the filling funnel in the side neck of the boiling flask and the separatory funnel in the center neck. Insert the condenser in the top joint of the separatory funnel. Connect the condenser to a source of cooling water. Use a ringstand and clamp to position the assembly.

2. Arsine generator. Fisher Scientific Co. catalogue No. 1-405. This consists of a 125-ml. Erlenmeyer flask, a scrubber unit and an absorber unit with $\frac{1}{2}$ or $\frac{3}{4}$ joints between the units.
3. Spectrophotometer, Beckman Model DU (or other instrument suitable for measurement at 525 millimicrons) equipped with 10 mm. pathlength cells.

Reagents

1. Sulfuric acid, concentrated.
2. Nitric acid, concentrated.
3. Perchloric acid 70%.

4. Silver diethyldithiocarbamate-pyridine solution. Dissolve 1 g. of silver diethyldithiocarbamate in 200 ml. of pyridine. Store in an amber bottle.
5. Stannous chloride solution. Dissolve 40 g. of stannous chloride in 100 ml. of concentrated hydrochloric acid.
6. Zinc metal. Low arsenic, 20 mesh, Fisher No. Z-15.
7. Potassium iodide solution, 15%.
8. Lead acetate solution 15%.
9. Carborundum chips.
10. Arsenic stock solution, 0.100 mg./ml. (Solution A). Weigh 0.1320 g. of arsenic trioxide, dissolve in 10 ml. of 40% sodium hydroxide solution, and dilute to one liter with water.
11. Arsenic standard 1 microgram/ml. (Solution B). Dilute 10 ml. of Solution A to one liter with water.
12. Hydrochloric acid, concentrated.
13. Stopcock grease. Dow Corning Silicone.

Preparation of Calibration Curve

Measure 0, 3, 6, 9, 12, and 15 ml. of solution B into 125-ml. Erlenmeyer flasks and dilute each to 35 ml. with water. Add 5 ml. of conc. hydrochloric acid, 2 ml. of potassium iodide solution, and 8 drops of stannous chloride solution. Swirl the flasks and allow them to stand for 15 minutes. Meanwhile, place cotton moistened with lead acetate solution in the scrubber and 5.00 ml. of silver diethyldithiocarbamate solution in the absorber tube. Lubricate all joints with silicon stopcock grease. Chill the sample, add 3 g. of zinc and immediately assemble the arsine generator. Allow the reaction and evolution to continue for 30 minutes. Transfer the absorbing solution to the cell and measure the absorbance at 525 m μ . Plot absorbance vs. arsenic concentration in micrograms arsenic/5 ml.

Procedure

Accurately weigh 1 to 2 g. of sample into the boiling flask. Add 5 ml. conc. sulfuric acid and a boiling chip. Assemble the digestion apparatus. Add 5 ml. of conc. nitric acid to the filling funnel and introduce 0.5-1.0 ml. of it into the digestion flask. Heat gently, adding more nitric acid dropwise as the digestion proceeds. Adjust conditions to maintain nearly concentrated sulfuric acid in the digestion flask and continue until the liquid is almost colorless. Add perchloric acid dropwise through the filling funnel until 0.5 to 1.0 ml. have been

introduced. Heat the solution strongly for 5-10 minutes, then cool. Open the stopcock of the separatory funnel and drain the condensate into the flask. Transfer the contents of the flask to a 250-ml. beaker and heat to drive off most of the perchloric acid. Cool, add 10 ml. of water and boil for several minutes. Transfer the solution to the arsine generator flask and dilute to 35 ml. with distilled water. Continue as described under Preparation of Calibration Curve starting with " , 2 ml. of potassium iodide solution". Determine the micrograms of arsenic in the sample by comparison with the calibration curve.

Calculation

$$\text{ppm Arsenic} = \frac{\text{micrograms arsenic}}{\text{g. of sample}}$$

Reference

1. Anal. Chem. 31, 1589, 1593, 2052 (1959).

General Analytical Group II
August 1965

amb

AF 17-081

January 3, 1966

David Kaufman, Ph.D.
Technical Director
David A. Cook
Division of American
Chemical Company
Danbury, Connecticut 06813

Dear Dr. Kaufman:

We acknowledge receipt of your letter of December 23, 1965 and the accompanying certified check for \$4800. With receipt of this \$2600, your total deposit is now \$5200.

There appears to be a misunderstanding in your summary of your position. Petitions for H&B Blue No. 9 and Cobalt, chromium, and iron oxide pigments have been filed. We are still awaiting a method for identifying iron-pyrogallol dye on suture sutures.

Sincerely yours,

D. J. Miller, Deputy Director
Division of Color Certification & Evaluation

cc: CCE(Link)(Suture File)

DJMiller:smb 1/3/66
RD Sgd DJMiller

Color Division
CERAMIC • GLASS • PLASTIC

FERRO CORPORATION

COLOR DIVISION HEADQUARTERS
4150 EAST 56th STREET
CLEVELAND, OHIO 44105



February 1, 1966

Mr. David T. Miller
Deputy Director
Division of Color Certification & Evaluation
Food & Drug Administration
Department of Health, Education and Welfare
Washington, D. C. 20204

Re: Regulation for Color Additive for Coloring Linear Polyethylene
Surgical Sutures (Davis & Geck Division of American Cyanamid
Petition)

Dear Mr. Miller:

We are glad that a regulation is in preparation regarding the use of a color additive such as Ferro's Blue-Green Pigment F-5272 for coloring linear polyethylene surgical sutures.

We understand the necessity to identify the color additive and agree to reveal the proposed confidential information as outlined under "Identity" and "Specifications" paragraphs.

I would like to suggest slight changes in the wording of the first sentences in both paragraphs.

Instead of:

"(a) Identity . The color additive chromium, cobalt, aluminum oxide is a blue pigment, etc.",

I suggest to use:

"(a) Identity . The color additive chromium oxide-cobalt oxide - aluminum oxide is a blue-green pigment etc."

And, instead of:

"(b) Specifications . Chromium, cobalt, aluminum oxide shall conform to the following specifications: etc." I suggest to use:

"(b) Specifications . The color additive chromium oxide-cobalt oxide-aluminum oxide shall conform to the following specifications: etc."

These changes would, in my opinion, more accurately describe and identify the nature of the color additive which is not a chromium metal, cobalt metal and aluminum oxide composite but a solid solution of chromium oxide, cobalt oxide and aluminum oxide.

Mr. David T. Miller

-2-

February 1, 1966

The other restrictions and the 0.5 N hydrochloric acid extraction are O.K.

Very truly yours,



Aladar Burgyan
Director of Color R & D

AB:md

cc: Mr. David Kaufman
Davis & Geck
Division of American Cyanamid Co.
Danbury, Connecticut

- 062

MEMORANDUM OF INTERVIEW 5/3/66

PRESENT: William J. Tillman, Pharmaceutical Chemistry Section, and
Leon C. Greene, Director of Pharmaceutical Activities,
Federal Bacteriology Department,
Smith, Kline & French Laboratories
Philadelphia, Pennsylvania

David J. Miller, CCM

Drs. Greene and Tillman called after having previously talked to Dr. Goldenthal, DHE, about the use of certain dyes in surgical sutures.

Dr. Tillman told Smith, Kline and French Laboratories plan to purchase a firm manufacturing a suture coated with a coal-tar dye which is not provisionally listed. They wished to know what was the status of this dye. I told Dr. Tillman that if this was a coal-tar dye which was not entitled to provisional listing in 1960, then it could not be provisionally listed now and that all investigations would have to be completed, a petition submitted for permanent listing and a regulation issued before it could be authorized for use.

The discussion was enlarged to cover the status of presently provisionally listed color additives when used for sutures. I said that although a color additive may be considered to be provisionally listed for ingested and externally applied drug use it was not necessarily considered provisionally listed for suture use also. I said that in general we had adopted the policy that if the color additive had been in commercial use on a particular type suture, e.g., cotton, silk, etc., prior to the date of the enactment of the Color Additive Amendments (July 12, 1960) we would consider it provisionally listed for suture use but then only if studies were under way to establish its safety for suture use. I said we had not specifically indicated in the published provisional listings which color additives were authorized for use in sutures, on the basis that studies were under way, because we had not necessarily been informed of such studies. I said we considered D&C Blue No. 9 as provisionally listed for use on cotton and silk surgical sutures, D&C Red No. 30 on cotton sutures, D&C Green No. 5 on nylon sutures, leucod on silk and nylon sutures, pyrogallol and iron salts on catgut sutures, and chromium-cobalt-aluminum oxide on linear polyethylene sutures. I said D&C Green No. 6 was provisionally listed for use on cotton sutures. I said that we had had discussions with suture manufacturers about D&C Blue No. 6 and D&C Violet No. 2 but I had no positive assurance that studies were under way for these colors. In answer to a question by Dr. Tillman I said I did not think a color additive should be considered provisionally listed for suture use if no studies were under way to establish its safety even though studies were under way to establish safety for ingested and external

use. I said I did not think it would be in keeping with the spirit of the transitional sections of the Color Additive Amendments to keep a provisional listing going indefinitely just because periodically a user decided he had a new use for a color additive. I said the transitional sections of the Color Additive Amendments were intended for the transitional period was intended only to allow time for the investigations started immediately after the Color Additive Amendments were passed and that while we had been liberal in our approach because of the delay in issuing the color additive regulations we could not continue provisional listings indefinitely.

In response to questions from Dr. Greene I outlined briefly the requirements for pharmacological testing for color additives for suture use--that is, acute, subacute, parenteral and embolus studies. I said that if the FDA had made acute and subacute studies, the results would be made available to a petitioner.

There was a brief discussion of the new drug status of dyed sutures and I said that there could well be situations in which a petition for the use of a color additive in sutures would also involve either an original or supplemental new drug application.

There was some discussion of one user "riding on the coattails" of a second user who is a petitioner. I said that the listing of a color additive under certain conditions of use did not limit the use to the petitioner. I added that in the case of sutures, there was a possibility that the regulation listing the color additive would spell out the dyeing process if this were necessary to insure the safe conditions of use of the color additive and that if a suture manufacturer used a dyeing process different from the one spelled out in the regulations his use of the color additive would be illegal even though he may have used an identical straight color. I emphasized that the regulation would not necessarily describe the dyeing process but that it could, or that it might spell out specific mordants, etc.

David J. Miller, CCE _____

cc: TS (Dr. [redacted])
(Dr. Goldenthal)
Sci
VN
CCE (Mr. Link)
(Suture File)

000117

MEMORANDUM OF CONFERENCE

December 4, 1967

Between: Dr. David Kaufman, Technical Director
Davis & Geck,
Danbury, Connecticut
Dr. Harry D. Evans, Jr., Medical Director
Davis & Geck
Danbury, Connecticut

and

Mr. David J. Miller, Deputy Director
Div. of Color Certification and Evaluation
Dr. Charles J. Kokoski
Div. of Toxicological Evaluation

Dr. Kaufman and Dr. Evans called by appointment to discuss the status of 5 color additive petitions submitted by Davis & Geck but which had either not been filed or, if filed, the color additive involved had not been permanently listed. Mr. Miller said that no further information was needed for CAP No. 12, Chromium-cobalt-aluminum oxide in linear polyethylene sutures, or CAP No. 14, D&C Blue No. 9. Mr. Miller said that however, the new drug status of these two petitions, as well as the new drug status of the petitions discussed below had not been settled and that until a firm decision had been reached as to whether new drug applications were necessary, we were not ready to issue regulations listing the color additives for suture use. Discussions concerning other petitions were as follows:

CAP NO. 13 - PYROGALLOL AND IRON
SALT IN PLAIN AND CATGUT SUTURES
INCLUDING OPHTHALMIC SUTURES.

The petition is considered essentially complete. However, we said that we would like to see UV curves of the extracts from sutures from various batches of chromic and plain sutures using the analytical procedure submitted 12/13/66. We said we needed this information to show the reproducibility of coloring material from batch to batch. There was some discussion of the need for toxicity studies on the chromic sutures. (This type suture was the subject of an amendment to the original petition which involved plain catgut sutures only) Dr. Kaufman said he felt that the two-year imbedding studies made with the plain sutures would be equally applicable to the chromic sutures because the only difference was

000128

that the sutures were absorbed in about twenty days and the plain sutures in ten days. He said that under present policy it was permissible to add pyrogallol to the chromic sutures as a tanning aid and that the only further treatment was the addition of iron salt to increase the black color. Dr. Kaufman stated he had on file some toxicological data obtained from tensile strength implantation tests for chromic catgut sutures, which he would send us to assist in our evaluation.

CAP NO. 46 - D&C BLUE NO. 6
IN POLYESTER (DACRON) SUTURES

We said that we had no letter of authorization from National Aniline allowing Davis & Geck to refer to manufacturing processes for D&C Blue No. 6. We said we lacked certain information about intermediates and subsidiary colors in D&C Blue No. 6 but that in light of an anticipated petition by Pharmaceutical Manufacturers Association, we would not insist on specifications for D&C Blue No. 6 from Davis & Geck at this time. We said we felt we should have more information about stability of the color in the suture than had been submitted and suggested a reanalysis of samples of sutures previously analyzed. Dr. Kaufman said he was not sure whether he had such samples but would check when he returned to his office. He said he felt that checking the content before and after autoclaving is a more rigorous test than a room stability' one. Mr. Miller said that even if this were true, such information had not been furnished. Dr. Kaufman said that he also felt that insofar as stability in the body was concerned, the sutures after a two-year implantation study still showed an intense blue color and that this visual appearance was good evidence of stability. Dr. Kokoski said there were certain ambiguities in the toxicological data and pointed out an apparent typographical error in the title of one of the photomicrographs. On Page 31, Fig. 3B of a revised Subpart D submitted on July 3, 1967 the word "not" should read "most". He also mentioned that the toxicological report did not appear as complete as reports in the firm's other petitions. Further discussion indicated that some data submitted in 1964 prior to the actual submission of the petition had not been placed in the copy reviewed by Dr. Kokoski. It was stated that Dr. Kokoski would review this additional material.

CAP NO. 52 - FD&C BLUE NO. 2
IN NYLON SUTURES

We told Dr. Kaufman that his June 8, 1967 response to our questions about manufacturing processes and specifications was incom-

000129

plate, but that in light of an anticipated petition for FD&C Blue No. 6, the Garfiliated Color Industry Committee we would withhold any requests pending review of the data in the CCIC petition. We discussed the stability studies made by Davis & Geck and said we were not sure that the autoclaving conditions represented adequate testing of sutures either in storage or implanted in the human body. Dr. Kaufman said (as discussed under D&C Blue No. 6 above) that autoclaving was a more rigorous test, which, in the absence of significant losses, would prove the stability of the color additive both when stored in containers and in the human body. Dr. Kokoski said he would like to study the situation somewhat further before making any comments.

There was some discussion of closing dates of provisional listing. I pointed out that the closing date of the provisional listing of Blue No. 6 was December 31, 1967 and suggested that it would be desirable for Davis & Geck to request postponement of the closing date. Dr. Evans demurred since he felt that essentially the need for additional time was for the Food and Drug Administration to consider data already submitted or to prepare an order but then concluded that the firm would request a postponement of the closing date.

Dr. Kaufman asked about the status of studies for logwood on silk and cotton sutures. He was aware that Ethicon had withdrawn their petition for the listing of logwood. I said I did not know just where Ethicon was in their program -- that they had been in to see us in October and we had discussed protocols. I asked Dr. Kaufman if Davis & Geck had data and was prepared to submit a petition of their own. Dr. Kaufman indicated that they had considerable data but was not sure it was of the type satisfactory for a petition and also commented on the problem of preparing a petition and paying the necessary fee. I pointed out that the provisional listing of logwood was only until June 30, 1968 and that in the absence of work underway or a petition, I was not sure just what action the Commissioner would take about continued provisional listing. Dr. Kaufman, in response to a question, said industry competition would preclude filing of a joint petition with other suture manufacturers.

David J. Miller, DCE

cc: Postponement After Dec. 31, 1967
 Postponement After June 30, 1968
 DTE
 CAP No. 13 file
 CAP No. 46 file

000130

CAP No. 1011
CAP No. 1011
CAP No. 1011
DCCE(Link)

RD DJMiller:hvm

Final: DJMiller:hvm

RD Initialed: CJKokoski

MEMORANDUM OF CONVERSATION
April 11, 1968

Between: Dr. David Kaufman, Technical Director
David & Gock Co., Division of American Cyanamid Co.
Danbury, Connecticut

and

Mr. David J. Miller, Deputy Director
Division of Color Certification and Evaluation

Dr. Kaufman called to discuss the pending color additive petitions CAP No. 13, pyrogallol-iron in plain and catgut sutures, CAP No. 46, D&G Blue No. 6 in polyester (dacron) sutures and CAP No. 32, FD&C Blue No. 2 in nylon sutures.

Dr. Kaufman said he was leaving Davis & Gock in June and was trying to clean up "loose ends" in connection with color additive petitions. I read Smith's memorandum of conference of December 4, 1967 the additional information we had requested for the above petitions. Dr. Kaufman said that he hoped to supply this additional information before he left. I told Dr. Kaufman that with the submission of petitions for D&G Blue No. 6 by the Pharmaceutical Manufacturers Association and for FD&C Blue No. 2 by the Certified Color Industry Committee, we no longer were in need of manufacturing processes.

David J. Miller, DCC (DC-301)

cc: CAP No. 14 file
CAP No. 13 file
CAP No. 9 file
CAP No. 12 file
CAP No. 46 file
CAP No. 32 file

WJH: [illegible] 4/18/68

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000132

PUBLIC HEALTH SERVICE

December 19, 1968

CAR 12

Mr. J. Kevin Rooney, Director
Technical Services Branch
Office of Government Controls
Davis and Cook
Americana Cymnoid Company
Pearl River, New York 10965

Dear Mr. Rooney:

This is in reply to your letter of December 9, 1968 to Mr. David J. Miller about the status of certain color additive petitions.

We are not at this time requesting further chemical or animal pharmacological data for the following color additive petitions:

CAP No. 12 - Chromium, cobalt, aluminum oxide for coloring linear polyethylene sutures

CAP No. 13 - Pyrogallol plus iron salt for coloring plain and chronic catgut sutures, including ophthalmic sutures

CAP No. 14 - BHC Blue No. 9 for coloring cotton and silk sutures including ophthalmic sutures

Color Additive Petitions Nos. 46 for BHC Blue No. 6 for coloring polyester sutures and 52 for FHC Blue No. 2 for coloring nylon sutures are deficient with regards to certain chemical data. We are not at this time requesting you to furnish the missing data because we expect to receive this data from other sources.

We are not prepared to issue regulations listing any of the subject color additives for future use until the New Drug status of each suture has been determined. When a determination is made, we will contact you immediately.

We have requested the fiscal branch to refund the \$2,600 credited to the Davis and Cook account.

Sincerely yours,

William B. Link
Division of Colors and Cosmetics
Bureau of Science

cc: SC-1; SC-12; SC-970; MB-5(Dr. Palmer) SC-220(Link)
SC-220 WBLink:ash 12/19/68

000133

ALICE
CAP #12

Public Health Service

AP 12

April 28, 1969

Dr. J. Kevin Rooney, Director
Technical Services Branch
Office of Government Controls
Davis & Cook
American Cyanamid Company
Roslindale, New York 10065

Dear Dr. Rooney:

This is in reply to your letter of March 28, 1969 about the use of chromium-sorbit-aluminum oxide for coloring polypropylene sutures.

We cannot conclude at this time that the data in your CAP No. 12 for the use of chromium-sorbit-aluminum oxide as a color for linear polyethylene sutures will adequately support the listing of the color additive for use in polypropylene sutures. At this time we are not requesting long-term implantation studies such as were made with the polyethylene sutures. However, there should be some short-term (possibly 6 - 8 weeks) "over-over" toxicity studies to assess irritation or acute localized response. Further, in order to make a valid extrapolation of toxicity data you should provide information showing that the chemical and physical characteristics of polypropylene as compared with polyethylene -- e.g. molecular weights, crystallinity, catalysts, stabilizers, etc. -- are essentially the same. This information will be helpful in determining whether the migration of the colorant from the polypropylene would be any greater than from polyethylene.

Our comments are not to be construed as in any way waiving any "new drug" requirements for either the colored or uncolored sutures.

Sincerely yours,

David J. Miller
Acting Assistant Director
Division of Colors and Cosmetics
Bureau of Science

cc: MD-8(Dr. John Palmer)
SC-1, SC-970
SC-12, SC-230(Dr. Link)
SC-205 DJM:ham 4/28/69

Public Health Service

L. Kekoski
CAP 12

September 2, 1969

Doris R. Seeger, Ph.D.
Assistant Director
Medical Controls Branch
Office of Government Controls
Davis & Cook
American Cyanamid Company
Pearl River, New York 10965

Dear Dr. Seeger:

This is in reply to your letter of July 29, 1969 in which you asked for comments on a proposed protocol for a short-term toxicity study of chromium-cobalt-aluminum oxide colored polypropylene sutures.

In the last paragraph of my letter of April 28, 1969 to Dr. Rooney I indicated a "new drug" question might come up. Since writing that letter our Bureau of Medicine has advised me it considers the chromium-cobalt-aluminum oxide colored polypropylene suture to be a "new drug". Accordingly, any color additive listing of the chromium-cobalt-aluminum oxide to color polypropylene sutures would be dependent on there being an approved NDA.

In light of this situation I think it would be inappropriate for this division to comment on the proposed protocol. I have asked our Office of New Drugs, Bureau of Medicine to write to you about this matter.

Sincerely yours,

David J. Miller
Assistant Director
Division of Colors and Cosmetics
Bureau of Science

cc: SC-970(Dr. Kekoski)✓
MB-100
MB-5(Dr. John Palmer)
CAP No. 12

(SC-205) DJMiller:asb 9/2/69

000147

MEMORANDUM OF CONFERENCE
July 9, 1973

Visitor: Gordon Personaus Davis & Geck Div., American Cyanamid
FBA: Gerard L. McCowin DF-334
Subject: Color Additive Petition No. 4C0012 and 4C0013

Mr. Personaus requested the conference to discuss limitations in the May 16, 1973 order in the Federal Register concerning pyrogallol and ferric ammonium citrate (CAP 4C0013). He stated that his firm was having difficulty meeting the 3% by weight limitation placed on the amount of color additive which would be present in the suture. He presented a copy of a test method for the dye content in the sutures which he said was an improvement to the method presently in the petition.

He said that using the new method they were able to obtain values for the color concentration of less than 3% by weight in plain catgut sutures. However, all of the values obtained for chromic catgut sutures were above 3%. He stated that the amounts found for all batches of chromic catgut produced since May 16, 1973, were as follows:

3.15%
5.70%
5.89%
5.32%
4.40%
4.45%

In view of this data, he requested that the 3% by weight of the sutures limitation on the amount of color additive be raised. I advised that this could probably be done but that I was unsure as to exactly how.

The firm's petition for chromium-cobalt-aluminum oxide was also discussed. Personaus stated that the firm no longer has any interest in the petition to provide for the use of the color additive in propylene sutures. I advised him that we would consider the petition withdrawn but asked that he submit a letter for the record withdrawing the amendment to the petition.

Page 2 - Memorandum of Conference

On 7/1/73, I telephoned Mr. Parsons to advise him that he should submit a written request that the limitation on the amount of pyranine-tartric ammonium citrate complex permitted in sutures be raised. I suggested that he supply a specific limit which the firm felt could be met. I advised him that his request should be supported by the analytical methods and results showing the levels of the color additive normally present in the sutures.

I mentioned that our intention was to confirm the order of May 16, 1973 and to include in the confirmation an order increasing the amount of dye permitted in the sutures.

Gerard L. McCowin

GLMcCowin/bff/8-3-73

R/D/Intd. GLMcCowin 7-12-73

CCP BF-334
BF-330
BF-300
BF-152
BF-144
CC-1

000161

July 18, 1973

Mr. Gordon R. Personaus
Ladarla Laboratories
Pearl River, N.Y. 10965

Re: Color Additive Petition No. 12

Dear Mr. Personaus:

We are enclosing for your review a copy of a draft of an order as a possible response to your petition. We would appreciate your comments on the draft order.

We have not yet received a written request withdrawing the amendment to the petition concerning use of the color additive in polypropylene sutures. You had stated during our conference on July 9, 1973, that your firm was not currently interested in that use of the color and requested withdrawal of the amendment. We would suggest that a written request withdrawing the amendment be submitted.

Sincerely yours,

Gerard McCowin
Assistant to the Director
Division of Food and Color
Additives, BF-334

cc: BF-334 BF-330 BF-300 BF-144 BF-152 CC-1

CMC: [redacted] 7/18/73

July 31, 1973

Mr. Gordon R. Personaus
American Cyanamid Co.
Pearl River, New York 10965

Dear Mr. Personaus:

Re: Color Additive Petition No. 12

This is to acknowledge receipt of your letter of July 24, 1973 withdrawing the March 20, 1969, amendment to the subject petition.

We are in the process of finalizing action on CAP 12 by permanently listing chromium-cobalt-aluminum oxide for use in polyethylene sutures. A copy of the draft of the order was sent to you on July 18, 1973. We would appreciate any comments you may have concerning the draft order.

Sincerely yours,

Gerard McCowin
Assistant to the Director
Division of Food and Color
Additives, BF-334

cc: BF-334 BF-330 BF-300 BF-438 BF-152 CC-1

CLM: [redacted] 7/31/73

000170

May 21, 1974

Mr. Gordon R. Personae, Director
Technical Services Branch
American Cyanamid Company
Pearl River, New York 10963

Re: Color Additive Petition No. 12

Dear Mr. Personae:

This is in reference to your letter of April 10, 1974, concerning the analytical methodology to be used in determining the amount of color additive present in the finished sutures.

We would have no objection to the use of the method described in your letter as a screening procedure. However, we would caution that each batch of the sutures would be expected, and, in fact, required by the regulation, to comply with the limitations on the amount of color additive present in the sutures if the necessary analyses were made for their presence.

Sincerely yours,

Gerard L. McCowin
Assistant to the Director
Division of Food and
Color Additives, HFF-334

cc: HFF-334 HFF-330 HFF-300 HFF-436 HFF-152 HFC-1

GLMcCowin:wmb 5-21-74

000198

12

and this part require that the rates of assessment fixed for a particular marketing year shall be applicable to all assessable walnuts from the beginning of that year; and (2) the 1974-75 marketing year began August 1, 1974, and the rates of assessment hereinafter fixed will automatically apply to all such assessable walnuts beginning with that date.

The expenses and assessment rates are as follows:

§ 984.326 Expenses of the Walnut Marketing Board and rates of assessment for the 1974-75 marketing year.

(a) *Expenses.* Expenses in the amount of \$200,000 are reasonable and likely to be incurred by the Walnut Marketing Board during the marketing year beginning August 1, 1974, for its maintenance and functioning, and for such purposes as the Secretary may, pursuant to the provisions of this part, determine to be appropriate.

(b) *Rates of assessment.* The rates of assessment for said marketing year, payable by each handler in accordance with § 984.39, are fixed at 0.125 cent per pound for merchantable inshell walnuts and 0.30 cent per pound for merchantable shelled walnuts.

(Secs. 1-19, 48 Stat. 31, as amended; 7 U.S.C. 601-674)

Dated: October 24, 1974.

CHARLES R. BRADER,
Deputy Director, Fruit and
Vegetable Division.

[FR Doc. 74-25158 Filed 10-29-74; 8:45 am]

Title 21—Food and Drugs

CHAPTER I—FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

SUBCHAPTER A—GENERAL

PART 8—COLOR ADDITIVES

Chromium-Cobalt-Aluminum Oxide Pigment: Confirmation of Effective Date

An order was published in the FEDERAL REGISTER of August 7, 1974 (39 FR 28421), listing chromium-cobalt-aluminum oxide pigment for safe use in coloring sutures (21 CFR 8.601b) and deleting it from the list of color additives in § 8.501(f).

Pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (sec. 706 (b), (c), and (d), 74 Stat. 399-403; 21 U.S.C. 376 (b), (c), and (d)) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 2.120), notice is given that no objections or requests for hearing were filed in response to the subject order. Accordingly, the amendments promulgated thereby will become effective October 7, 1974.

Dated: October 22, 1974.

SAM D. FINE,
Associate Commissioner
for Compliance.

[FR Doc. 74-25158 Filed 10-29-74; 8:45 am]

PART 8—COLOR ADDITIVES

FD&C Red No. 40: Confirmation of Effective Date

An order was published in the FEDERAL REGISTER of August 6, 1974 (39 FR 28273), listing FD&C Red No. 40 as a safe color additive for use in dentifrices which are cosmetics subject to certification (21 CFR 8.7201).

Pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (sec. 706 (b), (c), and (d), 74 Stat. 399-403; 21 U.S.C. 376 (b), (c), and (d)) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 2.120), notice is given that no objections or requests for hearing were filed in response to the subject order. Accordingly, the amendment promulgated thereby will become effective October 7, 1974.

Dated: October 22, 1974.

SAM D. FINE,
Associate Commissioner
for Compliance.

[FR Doc. 74-25155 Filed 10-29-74; 8:45 am]

SUBCHAPTER B—FOOD AND FOOD PRODUCTS

PART 19—CHEESES, PROCESSED CHEESES, CHEESE FOODS, CHEESE SPREADS, AND RELATED FOODS

Label Requirements for Cottage Cheese Products

In a notice published in the FEDERAL REGISTER of June 3, 1974 (39 FR 19501), the Commissioner proposed that Part 19 be amended by deleting the undesignated paragraphs immediately following §§ 19.525(e)(3) and 19.530(e)(4).

The purpose of the proposal was to remove an inconsistency which exists between the standards for cottage cheese dry curd and cottage cheese under §§ 19.525 and 19.530 and the requirements of § 1.9d *Food labeling: information panel*, published in the FEDERAL REGISTER of March 14, 1973 (38 FR 6950). Since there is already in §§ 19.525(e) and 19.530(e) a cross-reference to the Part 1 requirements, deletion of the undesignated paragraph immediately following these paragraphs as proposed will remove the inconsistency.

No comments were received which responded to the issue raised in the proposal.

The only comment received, which was from a trade association, recommended that the term "dried milk" as used in § 19.530(e)(1) be revised to read "dry whole milk" to avoid confusion and to reaffirm the distinction between "dry whole milk" and "nonfat dry milk."

The subject raised by the one comment was not in response to the proposal; however it will be considered in response to the proposed revision of § 1.10 *Food labeling; designation of ingredients* published in the FEDERAL REGISTER of June 14, 1974 (39 FR 20888).

In the absence of any adverse comments to the proposal and because the

aforementioned undesignated paragraphs are not consistent in every respect with the requirements of § 1.8d(c), the Commissioner concludes that the paragraphs should be deleted.

Therefore, pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 401, 701, 52 Stat. 1046, 1055-1056, as amended by 70 Stat. 919 and 72 Stat. 948; 21 U.S.C. 341, 371) and under authority delegated to the Commissioner (21 CFR 2.120): *It is ordered*, That §§ 19.525(e) and 19.530(e) be revised to read as follows:

§ 19.525 Cottage cheese dry curd; identity; label statement of optional ingredients.

(e) The common or usual name of each of the ingredients used in the food shall be declared on the label as required by the applicable sections of Part 1 of this chapter, except that:

(1) Concentrated skim milk, nonfat dry milk, and reconstituted skim milk prepared by addition of water to concentrated skim milk or nonfat dry milk may be declared as "skim milk."

(2) Bacterial cultures may be declared by the word "cultured" followed by the name of the substrate, e.g., "made from cultured skim milk."

(3) Milk-clotting enzymes may be declared by the word "enzymes."

§ 19.530 Cottage cheese; identity; label statement of optional ingredients.

(e) The common or usual name of each of the ingredients used in the food shall be declared on the label as required by the applicable sections of Part 1 of this chapter, except that:

(1) Concentrated milk, dried milk, and reconstituted milk prepared by addition of water to concentrated milk or dried milk may be declared as "milk."

(2) Concentrated skim milk, nonfat dry milk, and reconstituted skim milk prepared by addition of water to concentrated skim milk or nonfat dry milk may be declared as "skim milk."

(3) Bacterial cultures may be declared by the word "cultured" followed by the name of the substrate, e.g., "made from cultured skim milk."

(4) Milk-clotting enzymes may be declared by the word "enzymes."

Any person who will be adversely affected by the foregoing order may at any time on or before November 29, 1974, file with the Hearing Clerk, Food and Drug Administration, Rm. 4-05, 5600 Fishers Lane, Rockville, MD 20852, written objections thereto. Objections shall show when the person filing will be adversely affected by the order, specify with particularity the provisions of the order deemed objectionable, and state the grounds for the objections. If a hearing is requested, the objections shall state the issues for the hearing, shall be supported by grounds factually and legally sufficient to justify the relief sought, and shall include a detailed description and

Effective date. This amendment shall become effective on August 7, 1974.

[SEAL] **VERNON D. ACHER,**
Commissioner of Customs.

Approved: July 22, 1974.

DAVID E. MACDONALD,
Assistant Secretary
of the Treasury.

[FR Doc. 74-17952 Filed 8-6-74; 8:45 am]

Title 21—Food and Drugs
CHAPTER I—FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

SUBCHAPTER A—GENERAL

PART 8—COLOR ADDITIVES

Chromium-Cobalt-Aluminum Oxide Pigment

The Commissioner of Food and Drugs, having evaluated the data in a petition (CAP 12) filed by Davis and Geck, Division of American Cyanamid Co., Danbury, CT 06813, and other relevant material, finds that chromium-cobalt-aluminum oxide pigment is safe under the conditions prescribed in this order for use in coloring linear polyethylene surgical sutures, U.S.P., for use in general surgery and that certification is not necessary for the protection of the public health.

Chromium-cobalt-aluminum oxide is currently provisionally listed in § 8.501 (f) (2) (21 CFR 8.501(f)) for use in polyethylene surgical sutures only. There are no other color additive petitions or progress reports, as required by the color additive regulations (21 CFR Part 8), for the use of chromium-cobalt-aluminum oxide in drugs. Accordingly, chromium-cobalt-aluminum oxide is being deleted from § 8.501 (f), effective on the effective date of this order.

Therefore, pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (sec. 706 (b), (c), and (d), 74 Stat. 399-403; 21 U.S.C. 376 (b), (c) and (d)) and the transitional provisions accompanying the Color Additive Amendments of 1960 (sec. 203, 74 Stat. 404-407; 21 U.S.C. 376 note) and under authority delegated to the Commissioner (21 CFR 2.120), Part 8 is amended as follows:

§ 8.501 [Amended].

1. In § 8.501(f) by deleting "Chromium-cobalt-aluminum oxide" from the list of color additives.

2. By adding the following new section to Subpart F:

§ 8.6010. Chromium-cobalt-aluminum oxide.

(a) *Identity.* The color additive chromium-cobalt-aluminum oxide is a blue-green pigment obtained by calcining a mixture of chromium oxide, cobalt carbonate, and aluminum oxide. It may contain small amounts (less than 1 percent each) of oxides of barium, boron, silicon, and nickel.

(b) *Specifications.* Chromium-cobalt-aluminum oxide shall conform to the following specifications:

Chromium, calculated as Cr_2O_3 , 34-37 percent.

Cobalt, calculated as CoO , 29-34 percent.

Aluminum, calculated as Al_2O_3 , 29-35 percent.

Lead (as Pb), not more than 30 parts per million.

Arsenic (as As), not more than 3 parts per million.

Total oxides of aluminum, chromium, and cobalt not less than 97 percent.

Lead and arsenic shall be determined in the solution obtained by boiling 10 grams of the chromium-cobalt-aluminum oxide for 15 minutes in 50 milliliters of 0.5 N hydrochloric acid.

(c) *Uses and restrictions.* The color additive chromium-cobalt-aluminum oxide may be safely used for coloring linear polyethylene surgical sutures, U.S.P., for use in general surgery, subject to the following restrictions:

(1) For coloring procedure, the color additive is blended with the polyethylene resin. The mixture is heated to a temperature of 500°-550° F. and extruded through a fixed orifice. The filaments are cooled, oriented by drawing, and set by annealing.

(2) The quantity of the color additive does not exceed 2 percent by weight of the suture material.

(3) The dyed suture shall conform in all respects to the requirements of the U.S.P.

(4) When the sutures are used for the purpose specified in their labeling, there is no migration of the color additive to the surrounding tissue.

(5) If the suture is a new drug, an approved new drug application, pursuant to section 505 of the Federal Food, Drug, and Cosmetic Act, is in effect for it.

(d) *Labeling.* The label of the color additive shall conform to the requirements of § 8.32.

(e) *Exemption from certification.* Certification of this color additive is not necessary for the protection of the public health, and batches thereof are exempt from the certification requirements of section 706(e), of the act.

Any person who will be adversely affected by the foregoing order may at any time on or before September 6, 1974, file with the Hearing Clerk, Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20852, written objections thereto. Objections shall show wherein the person filing will be adversely affected by the order, specify with particularity the provisions of the order deemed objectionable, and state the grounds for the objections. If a hearing is requested, the objections shall state the issues for the hearing, shall be supported by grounds factually and legally sufficient to justify the relief sought, and shall include a detailed description and analysis of the factual information intended to be presented in support of the objections in the event that a hearing is held. Objections may be accompanied by a memorandum or brief in support thereof. Six copies of all documents shall be filed. Received objections may be seen in the above office during working hours, Monday through Friday.

Effective date. This order shall become effective October 7, 1974, except as to any provisions that may be stayed by the filing of proper objections. Notice of the filing of objections or lack thereof will be announced by publication in the **FEDERAL REGISTER**.

(Sec. 706 (b), (c), and (d), 74 Stat. 399-403; 21 U.S.C. 376 (b), (c), and (d)) and the transitional provisions accompanying the Color Additive Amendments of 1960 (Sec. 203, 74 Stat. 404-407; 21 U.S.C. 376 (note)).

Dated: July 31, 1974.

SAM D. FINE,
Associate Commissioner
for Compliance.

[FR Doc. 74-17952 Filed 8-6-74; 8:45 am]

RULES AND REGULATIONS

FEDERAL REGISTER
OCTOBER 30, 1974
Page-38222

NO-ALCOHOL

Title 21—Food and Drugs ✓
CHAPTER I—FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH,
EDUCATION, AND WELFARE

SUBCHAPTER A—GENERAL

PART 8—COLOR ADDITIVES

Chromium-Cobalt-Aluminum Oxide
Pigment; Confirmation of Effective Date

An order was published in the FEDERAL REGISTER of August 7, 1974 (39 FR 28421), listing chromium-cobalt-aluminum oxide pigment for safe use in coloring sutures (21 CFR 8.6010) and deleting it from the list of color additives in § 8.501(f).

Pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (sec. 706 (b), (c), and (d), 74 Stat. 399-403; 21 U.S.C. 376 (b), (c), and (d)) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 2.120), notice is given that no objections or requests for hearing were filed in response to the subject order. Accordingly, the amendments promulgated thereby will become effective October 7, 1974.

Dated: October 22, 1974.

SAM D. FINE,
Associate Commissioner
for Compliance.

[FR Doc.74-25158 Filed 10-29-74; 8:45 am]

BF-160

AUG 6 1970

CAP #12

AF 17-081

Medical Controls Branch
Office of Government Controls
Davis & Gack
American Cyanamid Company
Attention: Doris R. Sawyer, Ph.D.
Pearl River, New York 10965

Dear Dr. Sawyer:

We apologize for our delay in commenting from the standpoint of a new drug on the suitability of the protocol for the short-term toxicity study submitted as an amendment to your Color Positive Petition No. 12. Specifically, this is your proposal for the coloring of polypropylene esters with chromium-cobalt-aluminum oxide.

In general, the fulfillment of requirements for the listing of a substance as a color additive will best insure for the same substance as a component of a new drug. In this regard, I am passing along the comments of the members of the Scientific Review Branch. It states that the protocol calls for testing a control polypropylene ester contaminated with chromium-cobalt-aluminum oxide. We further stipulated that the number of animals necropsied at each intra-rat sacrifice should be no less than four.

As a follow up to our conferences of December 4, 1969, and July 22, 1970, we are of the opinion that no long-term testing for carcinogenicity in animals is needed for the use of C.R.C. Green No. 6 when added in amounts of 0.1% to absorbable polyglycolic acid esters.

Sincerely yours,

William A. Gyarfas, M.D.
Director, Division of Surgical-Catal
Drug Controls
Office of Scientific Evaluation
Bureau of Drugs

cc:

NYR-30
30-100
30-160
30-22

R/D JEWilson(30-160)7/27/70

R/D Init. by JHuscoe 7/29/70; LJWallerre 8/3/70; and LCHarris 8/3/70.

Final Typed on 8/6/70

BF-160

Frederick J. Briggs, M.D.

RULES AND REGULATIONS

FEDERAL REGISTER
AUGUST 7, 1974
PAGE- 28421

2.1.3.2. *Salmonella*

SUBCHAPTER A—GENERAL

PART 5—COLOR ADDITIVES

Penjurn-Cobalt-Aluminum Oxide
Filter

Commissioner of Food and Drugs evaluated the data in a petition filed by Davis and Gust, Inc., American Cyanamid Co., and CT 00812, and also advised that it finds that chromium trioxide pigment is safe under the conditions prescribed in the color additive in coloring many petroleum products, U.S.P., for use in gas cylinders and that chromium trioxide is necessary for the production of the gas.

aluminum-cobalt-aluminum color
 this providing the listed in § 2.2
 of the 2.2.2.2. The use in red
 and green colors is not allowed
 for color additive petitions or
 reports, as required by the
 regulations (21 CFR Part 261)
 of aluminum-cobalt-aluminum
 color. According to the
 aluminum color is being d

000217

Mr. Gerad McCowin

April 10, 1974

re: Color Additive Petition No. 12

We are requesting at this time that you allow us to utilize the ash value as an alternative test procedure for determining satisfactory pigment content of the polyethylene sutures, when such value is found not to exceed 2.0%. If this be agreeable to you, the attached quality control specification TP-SM-39 could be incorporated as an addendum to Subpart C page 8 of our CAP 12 submission. The complete assay procedures as written would remain in effect for any samples which might yield an ash value exceeding the 2.0% maximum.

We would appreciate receiving your written approval of this procedure so that it can be made a part of our file on C.A.P. 12. If there are any questions regarding this matter, do not hesitate to contact me.

Sincerely yours,



Gordon R. Personeus, Director
Technical Services Branch
Office of Government Controls

GRP:rl
Attachment

DAVIS & GECK CYANAMID AMERICAN CYANAMID COMPANY DANBURY, CONNECTICUT TESTING PROCEDURES	PRODUCT POLYETHYLENE, BLUE LINEAR, PIGMENT CONTENT BY ASHING. vendor(s) ALL	SPECIFICATION NUMBER(S) TP-SM-39
PURCHASING UNIT	ORDERED BY	DIVISION CODE 9995
ISSUE DATE 3/11/74	REVISED	APPROVED

TITLE:

DETERMINATION OF PIGMENT CONTENT IN BLUE LINEAR
POLYETHYLENE SUTURE

PRINCIPLE:

The pigment content is determined by ashing blue polyethylene suture at 500° C. The ash is the pigment content.

APPARATUS:

Platinum dish
 Furnace, controllable at temperatures up to 500° C or above.
 Desiccator containing silica gel desiccant.

PROCEDURE:

1. Weigh 2 - 5g blue polyethylene suture (weight A). Place polyethylene suture in a weighed, dried and equilibrated (to room temperature) platinum dish (weight B).
2. Place dish with suture in a furnace at 200° C. Gradually increase the temperature and ignite at 500° C for a minimum of one hour. Continue until ash residue is blue and all the carbon is gone.
3. Let platinum dish with ash equilibrate to room temperature over silica gel before weighing (weight C).

CALCULATION:

$$\% \text{ Pigment content} = \frac{C - B}{A} \times 100$$

A = Weight of polyethylene in g.

B = Weight of platinum dish in g.

C = Weight of platinum dish and ash in g.

Prepared by

K. Banks
 K. Banks

Approved by

A. Feldbin
 A. Feldbin, Chief
 Chemical Control Laboratory

Approved by

J. Brokate
 J. Brokate, Manager
 Quality Control Department

15/11/74



April 10, 1974

Mr. Gerad McCowin
Assistant to the Director
Division of Food and Color Additives,
BF-334
Food and Drug Administration
200 C Street, Room 5327
Washington, D.C. 20204

re: Color Additive Petition No.1

Dear Mr. McCowin:

On February 27, 1974, we submitted to you our comments on the draft order for the above-referenced color additive petition submitted by our Davis and Geck on January 31, 1964. At this time we wish to bring to your attention a technical matter contained within our original petition which relates specifically to the determination of the color content in the suture but which has no direct bearing on the specifications as proposed in the draft order.

Essentially the methodology for the pigment determination contained therein stipulates that the suture sample be ignited to complete ash, followed by individual detailed analysis for determination of chromium cobalt and aluminum content. The sum total of these oxides representing dye content cannot exceed 2.0%.

Our experience to date has shown that the total ash content of our suture product invariably falls in the range of 0.6 - 0.7% which is well below the maximum allowable value. When the assay value obtained is in this range, it becomes redundant to proceed with the costly and time-consuming procedures to perform the three individual assays. This would also result in considerable savings of valuable suture material since the complete analysis requires 143 grams of suture material versus the need to use only 2-5 grams for the ash test. Also, release time for the sutures can be reduced from one month to one week by not having to perform the unnecessary testing.

CC: HFF-152 & 436
4/18/74

existing specification limits expanded on three items;

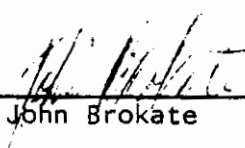
- 1) Co as CoO
- 2) Al as Al₂O₃
- 3) Extracted Pb.

The proposed specification would read as follows:

Co as CoO	← 29 - 34% ✓
Cr as Cr ₂ O ₃	34 - 37% ✓ same
Al as Al ₂ O ₃	→ 29 - 35% ✓
Ba as BaO	< 1% ✓
B as B ₂ O ₃	< 1% ✓
Ni as NiO	< 1% ✓
Si as SiO ₂	< 1% ✓
Extracted Pb	< 30 ppm ✓
Extracted As	< 3 ppm ✓

Please advise if the proposed change is acceptable.

JB/mh


John Brokate



Quality Control 2/21/74
OFFICE DATE

TO: Mr. G. Personeus - PR

LOCATION:

COPY TO: Mr. P. Cummings
Mr. A. Feldbin
Dr. J. McPherson
Mr. J. Riley
Mr. D. Sullivan
Mr. C. Schaffer

SUBJECT: Analysis of Polyethylene Pigment

REFERENCE:

For a period of time we have had problems purchasing pigment for our polyethylene sutures that would meet the pigment specifications as outlined in Color Additive Petition No. 12.

It is my understanding that recently the F.D.A. has been anxious to publish these specifications in the Federal Register. This department has requested a delay in the publication of any specifications until we had assurance these specifications could be met. It now appears that the specifications will have to be amended.

Listed below are the CAP-12 specifications, the analysis of a batch of pigment we are purchasing, and the analysis of two pigment batches that were used in the extrusion of polyethylene for the last five years. It should be noted that there has been no analysis done on pigment in the past; it was only the possible Federal Register publication of specifications that brought these requirements to our attention.

	CAP-12 Specification	Proposed Purchase	5 Year Production Lots	
			Lot 04-022-80	Lot 09-136-50
Co as CoO	30 - 33%	30.5%	30.7%	29.1%
Cr " Cr ₂ O ₃	34 - 37%	35.8%	36.7%	35.3%
Al " Al ₂ O ₃	28 - 31%	32.7%	31.7%	34.8%
Ba " BaO	<1%	<0.001 %	<0.001%	<0.001%
B " B ₂ O ₃	<1%	0.12%	0.11%	0.22%
Ni " NiO	<1%	0.27%	0.21%	0.24%
Si " SiO ₂	<1%	0.04%	0.02%	0.02%
Extracted Pb	<10 ppm	16 ppm	25 ppm	26 ppm
Extracted As	<3 ppm	2 ppm	2 ppm	2 ppm

The quantity of pigment we are about to purchase is 150 lbs. which should satisfy our requirements for a minimum of 15 years. Both Research and Development Dept. and the Quality Control Dept. would like to have the

Mr. Gerad L. McCowin

February 27, 1974

We regret very much the delay in getting this information to you. However, considerable effort in additional processing and analytical work was involved in this project prior to our being able to finalize our recommendations.

We look forward to your favorable reply regarding this proposal.

Sincerely yours,



Gordon R. Personeus, Director
Technical Services Branch
Office of Government Controls

GRP:rl
Attachment



February 27, 1974

Mr. Gerad L. McCowin
Assistant to the Director
Division of Food and Color
Additives, HFF-334
200 C Street - Room 5327
Washington, D.C. 20204

re CAP No. 12 Color Additive
Petition
Davis & Geck, American Cyanamid C

Dear Mr. McCowin:

On July 18, 1973 you kindly forwarded us a copy of the draft order on the chromium-cobalt-aluminum oxide pigment for use in polyethylene sutures asking for comments. Subsequent to that, on October 31 you telephoned this office to indicate you were awaiting our comments which we had hoped to complete in December 1973.

Attached herewith are detailed analytical studies and comments by the manager of Quality Control at Davis and Geck indicating that the few batches of pigment used in the past and a large batch to be purchased for the intended use, vary slightly in several of the proposed specifications in the draft. This is in spite of the fact that a significant effort was made by the Ferro Company in cooperation with Davis and Geck, to further reduce extractables by several rework washing procedures. As Mr. Brokate points out, historically this pigment production by Ferro Company, our only source for the color, has been consistent within limits reasonably close to those set forth in the draft. In view of this, since no other source of the pigment is available, we are requesting that the Administration favorably consider the minor revisions proposed by Davis and Geck for incorporation into the listing prior to final publication.

cc To
HFF-431
HFF-152
3/4/74



July 24, 1973

Mr. Gerad L. McCowin
Assistant to the Director
Division of Petitions Processing
200 C Street (Room 5327)
Washington, D. C.

Re Color Additive Petition No. 12

Dear Mr McCowin:

On March 20, 1969, this office filed a letter with the Food and Drug Administration on our Color Additives Petition No. 12, requesting that the limitation in this petition be amended to provide for polypropylene as well as linear polyethylene. In confirmation of my verbal request on July 9, 1973, we hereby formally request that said amendment be withdrawn predicated on the fact that we anticipate utilizing this color for polyethylene only at this time.

If at a future date we desired to utilize this color for polypropylene sutures, a new Application to amend the final order when approved would be filed.

Sincerely yours,


Gordon R. Personeus, Director
Technical Services Branch
Office of Government Controls

GRP:rl

CC BF ~~911~~ 438
BF 152

JUL 31 1973





July 11, 1973

Mr. Gerad L. McCowin
Assistant to the Director
Division of Petitions Processing
200 C Street - Room 5327
Washington, D. C.

Re C.A.P. No. 12
American Cyanamid Company

Dear Mr. McCowin:

This is to confirm our conversation of July 9, 1973 in your office, during which we also discussed the status of Color Additive Petition No. 12, which you had mentioned was nearing completion for publication. I have been asked to inform you that you may proceed with publication of this petition on the basis that we at this time intend to utilize this color for polyethylene sutures only. Therefore, you may disregard our request to use the dye in polypropylene sutures.

If at some later date our interest were renewed for its use in polypropylene, it is my understanding we would be required to file an amendment to the order.

We appreciate your clarification in this matter.

Sincerely yours,

Gordon R. Personeus, Director
Technical Services Branch
Office of Government Controls

GRP:rl

CC: BF-152

BF-438

7/18/73

7/23/73



INTEROFFICE CORRESPONDENCE

Toxicology
Research Section July 22, 1969
OFFICE BLOG/TUBE RM# DATE

TO:

ATT'N. OF:

COPY TO:

SUBJECT: Proposed Protocol for Subchronic Toxicity
Studies of Pigmented Polypropylene Sutures

REFERENCE: Letter to Mr. Rooney from Mr. David J. Miller,
Food and Drug Administration, April 28, 1969

It is proposed that the following studies be carried out in order to satisfy Mr. Miller's request for "some short-term (possibly 6-8 weeks) 'cross-over' toxicity studies to assess irritation or acute localized response" with polypropylene sutures:

Three groups of rats (12 rats each group) with 3 treatments. It is proposed that these sutures will be implanted subcutaneously on the ventral surface. One and a half or two inches of suture material will be implanted in two sites each rat.

The treatments will be as follows:

- A. Polypropylene Suture, Pigmented
- B. Polypropylene Suture, Not Pigmented
- C. Polyethylene Suture, Boxed Stock

The polypropylene and polyethylene sutures will be Size 3/0.

The three groups of rats will receive treatment as follows:

	<u>Treatment</u> (2 implantation sites)	<u>Sacrifice</u>
Group I (12 rats)	A and C	4 rats each group (8 implantation sites) will be sacrificed at the end of 1 week, 4 weeks, and 8 weeks.
Group II (12 rats)	A and B	
Group III (12 rats)	B and C	

The rats will be examined periodically for clinical signs of irritation or localized response. At the time of sacrifice, implant sites will be examined grossly and then excised for microscopic examination.

In addition, at the time of sacrifice the internal organs of the rats will be examined for any possible gross morphologic abnormalities.

JFN:kia

CJL
JCE

DAVIS & GECK

AMERICAN CYANAMID COMPANY
PEARL RIVER, NEW YORK 10865 TEL: 914 735-5000

July 29, 1969

Mr. David J. Miller
Acting Assistant Director
Division of Colors and Cosmetics
Bureau of Science
Department of Health, Education
and Welfare
Public Health Service
Washington, D. C. 20204

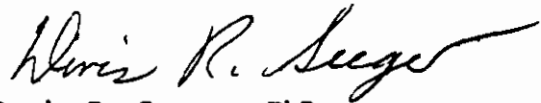
C.A.P. #12

Dear Mr. Miller:

As agreed in our telephone conversation of July 24, we submit for your consideration a proposed protocol for a short-term toxicity study in rats to assess irritation or acute localized response to polypropylene sutures colored with chromium-cobalt-aluminum oxide. We appreciate your offer to comment on the adequacy of the protocol to satisfy your April 28, 1969 request for animal toxicology to support the listing of the color additive for use in polypropylene sutures.

We await your opinion.

Sincerely yours,



Doris R. Seeger, PhD
Assistant Director
Medical Controls Branch
Office of Government Controls

DRS:cc

Enclosure



DAVIS & GECK

AMERICAN CYANAMID COMPANY
PEARL RIVER, NEW YORK 10985 TEL: 914 738-9000

DP#
Comment?
Spencer
Sc 200

March 20, 1969

Mr. William B. Link
Division of Colors and Cosmetics
Bureau of Science
Department of Health, Education
and Welfare
Public Health Service
Washington, D. C. 20204

C. A. P. #12

Dear Mr. Link:

Our Color Additives Petition #12 provides for the use of chromium, cobalt, aluminum oxide for coloring linear polyethylene sutures. We would propose amending this Application to allow for the coloring of polypropylene sutures in addition to polyethylene sutures. The polypropylene utilized is Moplene, Type F040. This is a food-grade, general purpose polyethylene supplied by the Novamont Corporation of New York City.

The information contained in this Color Additives Petition, as pertains to polyethylene in regards methods of manufacture, test methods, limits, etc., is equally applicable to polypropylene in that these two items are similar in composition and serve the same purpose when utilized as sutures.

We would therefore request that the limitation in this Petition be amended to provide for polypropylene as well as linear polyethylene sutures.

Very truly yours,


J. Kevin Rooney, Director
Technical Services Branch
Office of Government Controls

JKR:amt

