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Note To : John E. Bailey, Ph.D. (HFS-100)
Director
Office of Cosmetics and Colors

From : Stanley R. Milstein, Ph.D. (HFS-101) SRM
Special Assistant to the Director
Office of Cosmetics and Colors (OCAC)

Subject : **TALC SYMPOSIUM - SUGGESTED COSMETIC COMMENTS**

This note provides you with suggested comments for Dr. Gilbertson's ISRTP Workshop presentation on Talc, dealing with cosmetic perspectives.

Background

Talc, a complex hydrated magnesium silicate mineral, has been mined since the time of the ancient Greeks (Hildick-Smith) and has a history of being mined in several regions of the world, including Europe (esp. France and Italy), the Orient (including Manchuria and Japan), India, and the United States (including California, Montana, North Carolina, and Alabama). The cosmetic literature reports (whether accurately or not) that Italian cosmetic talc has been the western world's standard for centuries (Mulryan).

According to a now-dated U.S. Bureau of Mines estimate from 1979, the world's talc industry produced nearly 6.9 million tons of talc per year with a market value of ca. $ 435,000,000 (Kirk-Othmer). Of this total, ca. 17% of which could be expected to be of cosmetic quality (Mulryan).

Because cosmetic and pharmaceutical (OTC) product matrices that employ cosmetic talc are also expected to possess desirable aesthetic characteristics that will find widespread consumer acceptance, high quality cosmetic talcs...regardless of their geographic source, share three (3) common characteristics: high chemical purity, a clean white color, and good "slip", in addition to "softness" (Mohs Mineralogical Scale grade of 1) and acceptable texture. It has been said that a good quality talc should have such particle fineness that 98% of it goes through a standard 200-mesh sieve (i.e., 98% of the particles are sized < 74 microns); however, ultrafine grades of talc can also be produced and micronized talcs having particle sizes of only a few microns are also commercially available (Martin).

Uses of Talc

Talc is used in cosmetic products for the special "feel", "shine" and appearance (esp. "transparency" in face powders) that it imparts to the cosmetic formulation. A good talc should adhere to the skin evenly and aid in concealing superficial skin imperfections. Because of its softness and slip (lubricity), the

talc may also have an emollient effect on the skin, resisting mechanical abrasion and chafing of the skin, due to the rubbing of skin-skin or clothing-skin. The surface area of a talc also affects its ability to reflect light incident on the skin and, therefore, may also relate to its ability to reduce the perceived intensity or tint of a colorant. Chemically surface-treated ultra fine talcs can also afford water resistance in a cosmetic or OTC formulation.

Under the Federal Food Drug and Cosmetic Act (FDCA) of 1938, there is no requirement for premarket approval of cosmetics or, with the exception of color additives and a short "negative list" of prohibited substances given at 21 CFR 700, their constituent raw materials. Because there is no mandatory reporting requirement, FDA does not know exactly how many products are on the market that contain talc as an ingredient. However, FDA does maintain a Voluntary Registration Program (CVRP) for cosmetics (c.f., 21 CFR 720), in which companies can report their finished products and qualitative disclosures of ingredient composition.

The current CVRP database indicates that there are about 2000 products in some 45 different cosmetic product categories that are voluntarily registered with FDA. A few examples may be illustrative. There are only 7 products registered as "baby products" (baby lotions/ oils/ powders/ and creams), while under the more generic "powders" category, we find 425 products (21%) registered. More still are registered under the heading of "blushers, face powders, and foundations" where we find an additional 665 products (33.2%). Finally, there are 9 "men's talcum products" and 35 "foot powders".

It should be emphasized that this is not an exhaustive recounting of all cosmetic products or even of all product categories known to utilize talc. Nor does it represent the total universe of products or manufacturers of talc-containing cosmetic products in the industry. It is likely, however, that these registrations represent a significant portion of the volume of cosmetic products utilizing talc and distributed in the United States.

Based upon the figures given, as one surveys the product categories in which talc has been reported to be used, it seems clear that a significant number of cosmetic products are marketed at present for which there is a clear possibility of inhalation or perineal exposure.

Talc - Chemistry and Specifications

Talc has been described rather poetically as resulting "... during intense geologic upheavals underground, (which cause) torrents of magnesia-rich hot waters (to alter) basic rocks to hydrous magnesium silicate..." (Mulryan). The type of parent rock and the degree of alteration determine the purity and particle structure

of the talc. According to the CTFA specification for cosmetic talc, the balance of the talc may consist of other naturally occuring minerals such as calcite, chlorite, dolomite, kaolin, and magnesite.

Prior to the early 1970's, there was some concern that talc mined and processed commercially could be contaminated by asbestos or asbestiform minerals. Since that time, however, the cosmetic industry specification for talc has been tightened to virtually eliminate that concern. For example, a 1977 investigation of 46 talc samples by FDA revealed only 3 to contain asbestos (tremolite or anthophyllite), and even then the level was only 0.1% or less.

As mentioned earlier, there are no premarket approval requirements under FDCA for cosmetics or their constituent raw materials. Accordingly, there are no FDA-mandated regulatory standards or specifications for the grade of talc that may be used in formulating cosmetic products. However, the Agency did note in its discussion concerning talc as a Category I skin protectant ingredient for the prevention of diaper rash (c.f., 55 FR 25224, June 20, 1990) that:

"....cosmetic talc should contain at least 90% platy talc (having flat as opposed to fibrous particles) that is free of detectable amounts of fibrous minerals, including asbestos...".

Other general talc specifications have been published by the U.S. Pharmacopoeia, which specifies impurity limits, and by the CTFA (Cosmetic, Toiletry, and Fragrance Association), which now also dictates that there should be no detectable fibrous amphiboles such as asbestiform tremolite. (OSHA defines 'fibers' as particles of the relevant minerals which are 5 micometers or longer and having an aspect ratio of at least 3:1; c.f., 57 FR 24315, June 8, 1992). There is also a Food Chemicals Codex (FCC) talc specification, but the Agency has no way of knowing whether any given company in the cosmetic industry employs talc conforming to the USP, CTFA, or FCC specification. Parenthetically, we might note that ASTM has also published a talc standard for paints (Standard D-605-69).

Acute and Chronic Medical Consequences of Talc Use

The literature records that some pediatric authorities have recommended that the use of talcum powder (one of whose main constituents is talc) should be discouraged on neonates due to the possibility of acute massive inhalation-associated infant death. Some recent epidemiological studies, which have generated considerable public interest, have suggested an association between chronic female perineal talc dusting and the subsequent development of ovarian cancer. Also, there have been occasional occupational reports of chronic inhalation of talc dusts associated with the subsequent development of pulmonary fibrosis.

It is beyond the scope of this presentation to do more than take note of these medical and/or occupational consequences, alleged or proven, that may be associated with talc usage, and which have come to FDA's attention as well as to the attention of the American Public. We look forward to the full and authoritative discussion of these issues and others which will take place at this Symposium.

I recognize that there may be aspects of these comments that Dr. Gilbertson may wish to avoid as an FDA spokesperson, but I believe that there is enough given herein under the heading of "cosmetic perspectives" to allow for some judicious editing, as you may think best.

SRMilstein

2,4,6(1*H*,3*H*,5*H*)-Pyrimidinetrione, 5-(1-methylpropyl)-5-(2-propenyl)-,
5-Allyl-5-*sec*-butylbarbituric acid [*115-44-6*]

» Talbutal contains not less than 98.0 percent and not more than 102.0 percent of $C_{11}H_{16}N_2O_3$, calculated on the dried basis.

Packaging and storage—Preserve in tight containers.

Reference standard—*USP Talbutal Reference Standard* Dry in vacuum at 60° for 4 hours before using.

Identification—

A: The infrared absorption spectrum of a potassium bromide dispersion of it, previously dried, exhibits maxima only at the same wavelengths as that of a similar preparation of USP Talbutal RS.

B: The ultraviolet absorption spectrum of a 1 in 67,000 solution in pH 9.6 alkaline borate buffer (see under *Solutions* in the section, *Reagents, Indicators, and Solutions*) exhibits maxima and minima at the same wavelengths as that of a similar solution of USP Talbutal RS, concomitantly measured, and the respective absorptivities, calculated on the dried basis, at the wavelength of maximum absorbance at about 241 nm do not differ by more than 3.0%.

Loss on drying ⟨731⟩—Dry it in vacuum at 60° for 4 hours: it loses not more than 1.0% of its weight.

Residue on ignition ⟨281⟩: not more than 0.2%.

Heavy metals, *Method II* ⟨231⟩: 0.002%.

Assay—Transfer about 500 mg of Talbutal, accurately weighed, to a 125-mL conical flask, and dissolve in 25 mL of dimethylformamide. Add 5 drops of a freshly prepared 1 in 1000 solution of azo violet in dimethylformamide, and titrate with 0.1 *N* lithium methoxide VS to a blue-violet end-point, taking precautions against the absorption of atmospheric carbon dioxide. Perform a blank determination, and make any necessary correction. Each mL of 0.1 *N* lithium methoxide is equivalent to 22.43 mg of $C_{11}H_{16}N_2O_3$.

Talbutal Tablets

» Talbutal Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{11}H_{16}N_2O_3$.

Packaging and storage—Preserve in tight containers.

Reference standard—*USP Talbutal Reference Standard* Dry in vacuum at 60° for 4 hours before using.

Identification—Shake a quantity of finely powdered Tablets, equivalent to about 200 mg of talbutal, with 10 mL of pentane for 5 minutes, and filter through a medium-porosity, sintered-glass filter. Discard the filtrate, and shake the residue with 10 mL of chloroform for 15 minutes. Filter through the same filter, evaporate the filtrate with the aid of gentle heat to dryness, and use the residue of talbutal so obtained for the following tests.

A: A portion of the residue responds to *Identification test A* under *Talbutal*.

B: To the remainder of the residue add 1 mL of glacial acetic acid and 10 mL of water, mix, then add bromine TS dropwise: the bromine color is discharged on shaking.

Dissolution ⟨711⟩—

Medium: water; 900 mL.

Apparatus 2: 50 rpm.

Time: 45 minutes.

Procedure—Determine the amount of $C_{11}H_{16}N_2O_3$ dissolved from ultraviolet absorbances at the wavelength of maximum absorbance at about 241 nm of filtered portions of the solution under test, suitably diluted with pH 9.6 alkaline borate buffer (see under *Buffer Solutions* in the section, *Reagents, Indicators, and Solutions*), in comparison with a Standard solution having a known concentration of USP Talbutal RS in the same medium.

Tolerances—Not less than 75% (*Q*) of the labeled amount of $C_{11}H_{16}N_2O_3$ is dissolved in 45 minutes.

Uniformity of dosage units ⟨905⟩: meet the requirements.

Assay—

Standard preparation—Dissolve an accurately weighed quantity of USP Talbutal RS in 5 mL of alcohol contained in a 100-mL volumetric flask, dilute with pH 9.6 alkaline borate buffer (see under *Solutions* in the section, *Reagents, Indicators, and Solutions*) to volume, mix, and dilute quantitatively and stepwise with the same alcohol-buffer mixture to obtain a solution having a known concentration of about 10 µg per mL.

Assay preparation—Weigh and finely powder not less than 20 Talbutal Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 50 mg of talbutal, to a separator with the aid of 15 mL of water, and add 5 mL of 3 *N* hydrochloric acid. Extract with four 25-mL portions of chloroform, filter each portion through chloroform-washed cotton into a 250-mL volumetric flask, dilute with chloroform to volume, and mix. Transfer 5.0 mL of this solution to a beaker, and evaporate just to dryness. Transfer the residue to a 100-mL volumetric flask with the aid of, first, 5 mL of alcohol, and then pH 9.6 alkaline borate buffer. Dilute with the buffer to volume, and mix.

Procedure—Concomitantly determine the absorbances of the *Standard preparation* and the *Assay preparation* in 1-cm cells at the wavelength of maximum absorbance at about 241 nm, with a suitable spectrophotometer, using a 1 in 20 solution of alcohol in pH 9.6 alkaline borate buffer as the blank. Calculate the quantity, in mg, of $C_{11}H_{16}N_2O_3$ in the portion of Tablets taken by the formula:

$$5C(A_U/A_S),$$

in which C is the concentration, in µg per mL, of USP Talbutal RS in the *Standard preparation*, and A_U and A_S are the absorbances of the *Assay preparation* and the *Standard preparation*, respectively.

Talc

» Talc is a native, hydrous magnesium silicate, sometimes containing a small proportion of aluminum silicate.

Packaging and storage—Preserve in well-closed containers.

Identification—Mix about 200 mg of anhydrous sodium carbonate with 2 g of anhydrous potassium carbonate, and melt in a platinum crucible. To the melt add 100 mg of the substance under test, and continue heating until fusion is complete. Cool, and transfer the fused mixture to a dish or beaker with the aid of about 50 mL of hot water. Add hydrochloric acid to the liquid until effervescence ceases, then add 10 mL more of the acid, and evaporate the mixture on a steam bath to dryness. Cool, add 20 mL of water, boil, and filter the mixture: an insoluble residue of silica remains. Dissolve in the filtrate about 2 g of ammonium chloride, and add 5 mL of 6 *N* ammonium hydroxide. Filter, if necessary, and add dibasic sodium phosphate TS to the filtrate: a white, crystalline precipitate of magnesium ammonium phosphate separates.

Microbial limit—The total bacterial count does not exceed 500 per g.

Loss on ignition ⟨733⟩: Weigh accurately about 1 g, and ignite at 1000° to constant weight: it loses not more than 6.5% of its weight.

Acid-soluble substances—Digest 1.00 g with 20 mL of 3 *N* hydrochloric acid at 50° for 15 minutes, add water to restore the original volume, mix, and filter. To 10 mL of the filtrate add 1 mL of 2 *N* sulfuric acid, evaporate to dryness, and ignite to constant weight: the weight of the residue does not exceed 10 mg (2.0%).

Reaction and soluble substances—Boil 10 g with 50 mL of water for 30 minutes, adding water from time to time to maintain approximately the original volume, and filter: the filtrate is neutral to litmus paper. Evaporate one-half of the filtrate to dryness, and dry at 105° for 1 hour: the weight of the residue does not exceed 5 mg (0.1%).

Water-soluble iron—Slightly acidify with hydrochloric acid the remaining half of the filtrate obtained in the test for *Reaction*

and soluble substances, and add 1 mL of potassium ferrocyanide TS: the liquid does not acquire a blue color

Arsenic, Heavy metals, and Lead—

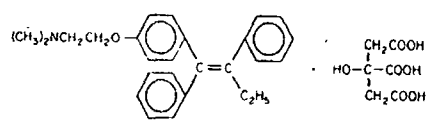
Test solution—Transfer 10.0 g to a 250-mL flask, and add 50 mL of 0.5 *N* hydrochloric acid. Attach a reflux condenser to the flask, heat on a steam bath for 30 minutes, cool, transfer the mixture to a beaker, and allow the undissolved material to settle. Decant the supernatant liquid through thick, strong, medium-speed filter paper into a 100-mL volumetric flask, retaining as much as possible of the insoluble material in the beaker. Wash the slurry and beaker with three 10-mL portions of hot water, decanting each washing through the filter into the flask. Finally, wash the filter paper with 15 mL of hot water, cool the filtrate to room temperature, dilute with water to volume, and mix. Use this *Test solution* for the following tests.

Arsenic, Method I ⟨211⟩—Use 10 mL of the *Test solution* in preparing the *Test Preparation*. The limit is 3 ppm.

Heavy metals ⟨231⟩—Use 5 mL of the *Test solution* in preparing the *Test Preparation*. The limit is 0.004%.

Lead ⟨251⟩—A 5-mL portion of the *Test solution* contains not more than 5 µg of lead (0.001%).

Tamoxifen Citrate



$C_{26}H_{29}NO.C_6H_8O_7$ 563.65

Ethanamine, 2-[4-(1,2-diphenyl-1-butenyl)phenoxy]-*N*,*N*-dimethyl-, (*Z*)-, 2-hydroxy-1,2,3-propanetricarboxylate (1:1).

(*Z*)-2-[*p*-(1,2-Diphenyl-1-butenyl)phenoxy]-*N*,*N*-dimethylethylamine citrate (1:1) [*54965-24-1*].

» Tamoxifen Citrate contains not less than 99.0 percent and not more than 101.0 percent of $C_{26}H_{29}NO.C_6H_8O_7$, calculated on the dried basis.

Packaging and storage—Preserve in well-closed, light-resistant containers.

Reference standard—*USP Tamoxifen Citrate Reference Standard*—Dry at 105° for 4 hours before using.

Identification—

A: The infrared absorption spectrum of a potassium bromide dispersion of it exhibits maxima only at the same wavelengths as that of a similar preparation of USP Tamoxifen Citrate RS, exhibiting a single band in the 1700 to 1740 cm^{-1} region of the spectrum.

B: The ultraviolet absorption spectrum of a 1 in 50,000 solution in methanol exhibits maxima and minima at the same wavelengths as that of a similar solution of USP Tamoxifen Citrate RS, concomitantly measured.

Melting range ⟨741⟩: melts at about 142°, with decomposition.

Loss on drying ⟨731⟩—Dry it at 105° for 4 hours: it loses not more than 0.5% of its weight.

Residue on ignition ⟨281⟩: not more than 0.2%.

***E*-isomer**—

Mobile phase—Prepare a methanol solution containing, in each liter, 320 mL of water, 2 mL of glacial acetic acid, and 1.08 g of sodium 1-octanesulfonate.

Standard preparation—Dissolve a suitable quantity, accurately weighed, of USP Tamoxifen Citrate RS in *Mobile phase* to obtain a solution having a known concentration of about 600 µg per mL.

Test preparation—Using about 30 mg of Tamoxifen Citrate, accurately weighed, proceed as directed under *Standard preparation*.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4-mm × 30-cm column that contains packing L11. The flow rate is about 0.7 mL per minute. Chromatograph five replicate injections of the *Standard preparation*, and record the resp... of the major peak: the relative standard deviation is not ... than 3.0% and the relative retention time of the minor *E*-iso... peak to that of the *Z*-isomer peak is not greater than 0.93.

Procedure—Separately introduce equal volumes (about 20 ... of the *Test preparation* and the *Standard preparation* into ... liquid chromatograph by means of a suitable sampling v... Measure the minor peak responses for the *E*-isomer obtained ... the *Standard preparation* and the *Assay preparation*. Calcu... the quantity, in mg, of *E*-isomer ($C_{26}H_{29}NO.C_6H_8O_7$) in ... portion of Tamoxifen Citrate taken by the formula:

$$0.05C(r_U/r_S),$$

in which C is the concentration, in µg per mL, of the *E*-iso... as the citrate, based on its declared content in USP Tamox... Citrate RS in the *Standard preparation*, and the r_U and r_S ... the minor peak responses obtained from the *Assay prepara...* and the *Standard preparation*, respectively. The *E*-isomer ... tent is not more than 1.0% of tamoxifen citrate ($C_{26}H_{29}N$... $C_6H_8O_7$).

Related impurities—

Test preparation A—Disperse about 3 g in 100 mL of w... in a separator. Over a 10-minute period add 50 mL of 0.... sodium hydroxide, with mixing. Extract with two 50-mL port... of ether, and combine the extracts. Wash with 20 mL of wa... remove the water layer, and dry the ether layer over anhydr... sodium sulfate. Evaporate the ether layer under nitrogen, ... dry in vacuum at room temperature for 2 hours. Accura... weigh 1.5 g of the residue into a 10-mL volumetric flask, ... 5.0 mL of a mixture of 5 volumes of acetic anhydride and ... volumes of pyridine, and heat at 60° for 10 to 15 minutes. Co... dilute with the same solvent mixture to volume, and mix.

Test preparation B—Using the same acetic anhydride–py... dine mixture, prepare a 1:200 dilution of *Test preparation ...*

Chromatographic system (see *Chromatography* ⟨621⟩)—T... ically, the gas chromatograph is equipped with a flame-ioniza... detector, and contains a 1-m × 4-mm glass column packed ... 5 percent liquid phase G17 on 100- to 120-mesh support S1... conditioned at 300° for 24 hours. The column and injection p... are maintained at about 260° and the detector at about 30... Dry helium is used as the carrier gas at a flow rate of abou... mL per minute. In a suitable chromatogram, five replicate ... jections of *Test preparation B* show a relative standard deviati... of not more than 3.0%.

Procedure—Inject equal portions (about 2 µL), accura... measured, of *Test preparation A* and *Test preparation B*, ... the chromatograph, and record the chromatograms from 0.... 5.0 relative to the retention time of the major peak. Measure ... individual areas of the peaks other than those produced by ... solvent and the tamoxifen on the chromatograms obtained ... *Test preparation A*, and calculate their sum. No single peak ... is greater than total area of the tamoxifen peak on the ... matogram obtained from *Test preparation B* (0.5%), and the ... of the peak areas is not greater than twice the total area o... tamoxifen peak on the chromatogram obtained from *Test p... aration B* (1.0%).

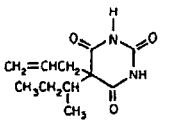
Iron ⟨241⟩—Accurately weigh 1.0 g, and transfer to a suit... crucible. Add sufficient sulfuric acid to wet the substance, ... carefully ignite at a low temperature until thoroughly char... (The crucible may be loosely covered with a suitable lid d... the charring.) Add to the carbonized mass 2 mL of nitric ... and 5 drops of sulfuric acid, and heat cautiously until white f... no longer are evolved. Ignite, preferably in a muffle furnace ... 500° to 600°, until the carbon is completely burned off. ... add 10 mL of warm 0.1 *N* hydrochloric acid, and digest for a ... 5 minutes. Transfer the contents of the crucible with the ac... small portions of water to a 50-mL volumetric flask, dilute ... water to volume, and mix. Pipet 10 mL from the volumetric ... into a color-comparison tube, dilute with water to 45 mL, a... mL of hydrochloric acid, and mix. The limit is 0.005%.

Arsenic, *Method II* ⟨211⟩—Use 10 mL of dilute sulfuric ac... in 2) instead of 5 mL of sulfuric acid. The limit is 2 ppm.

Heavy metals, *Method II* ⟨231⟩: 0.001%.

Assay—Weigh accurately about 1 g of Tamoxifen Citrate, ... dissolve in 150 mL of glacial acetic acid. Titrate the solu... with 0.1 *N* perchloric acid VS, determining the end-point p...

Talbutal



$C_{11}H_{16}N_2O_3$ 224.26

2,4,6(1*H*,3*H*,5*H*)-Pyrimidinetrione, 5-(1-methylpropyl)-5-(2-propenyl)-.

5-Allyl-5-*sec*-butylbarbituric acid [*115-44-6*].

» Talbutal contains not less than 98.0 percent and not more than 102.0 percent of $C_{11}H_{16}N_2O_3$, calculated on the dried basis.

Packaging and storage—Preserve in tight containers.

Reference standard—*USP Talbutal Reference Standard*—Dry in vacuum at 60° for 4 hours before using.

Identification—

A: The infrared absorption spectrum of a potassium bromide dispersion of it, previously dried, exhibits maxima only at the same wavelengths as that of a similar preparation of USP Talbutal RS.

B: The ultraviolet absorption spectrum of a 1 in 67,000 solution in pH 9.6 alkaline borate buffer (see under *Solutions*, in the section, *Reagents, Indicators, and Solutions*) exhibits maxima and minima at the same wavelengths as that of a similar solution of USP Talbutal RS, concomitantly measured, and the respective absorptivities, calculated on the dried basis, at the wavelength of maximum absorbance at about 241 nm do not differ by more than 3.0%.

Loss on drying ⟨731⟩—Dry it in vacuum at 60° for 4 hours: it loses not more than 1.0% of its weight.

Residue on ignition ⟨281⟩: not more than 0.2%.

Heavy metals, *Method II* ⟨231⟩: 0.002%.

Assay—Transfer about 500 mg of Talbutal, accurately weighed, to a 125-ml conical flask, and dissolve in 25 ml of dimethylformamide. Add 5 drops of a freshly prepared 1 in 1000 solution of azo violet in dimethylformamide, and titrate with 0.1 *N* lithium methoxide VS to a blue-violet end-point, taking precautions against the absorption of atmospheric carbon dioxide. Perform a blank determination, and make any necessary correction. Each ml of 0.1 *N* lithium methoxide is equivalent to 22.43 mg of $C_{11}H_{16}N_2O_3$.

Talbutal Tablets

» Talbutal Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{11}H_{16}N_2O_3$.

Packaging and storage—Preserve in tight containers.

Reference standard—*USP Talbutal Reference Standard*—Dry in vacuum at 60° for 4 hours before using.

Identification—Shake a quantity of finely powdered Tablets, equivalent to about 200 mg of talbutal, with 10 ml of pentane for 5 minutes, and filter through a medium-porosity, sintered-glass filter. Discard the filtrate, and shake the residue with 10 ml of chloroform for 15 minutes. Filter through the same filter, evaporate the filtrate with the aid of gentle heat to dryness, and use the residue of talbutal so obtained for the following tests.

A: A portion of the residue responds to *Identification test A* under *Talbutal*.

B: To the remainder of the residue add 1 ml of glacial acetic acid and 10 ml of water, mix, then add bromine TS dropwise: the bromine color is discharged on shaking.

Disintegration ⟨701⟩: 30 minutes.

Weight variation ⟨931⟩: meet the requirements for *Tablets*.

Assay—

Standard preparation—Dissolve an accurately weighed quantity of USP Talbutal RS in 5 ml of alcohol contained in a 100-ml volumetric flask, dilute with pH 9.6 alkaline borate buffer (see under *Solutions*, in the section, *Reagents, Indicators, and Solutions*) to volume, mix, and dilute quantitatively and stepwise with the same alcohol-buffer mixture to obtain a solution having a known concentration of about 10 µg per ml.

Assay preparation—Weigh and finely powder not less than 20 Talbutal Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 50 mg of talbutal, to a separator with the aid of 15 ml of water, and add 5 ml of 3 *N* hydrochloric acid. Extract with four 25-ml portions of chloroform, filter each portion through chloroform-washed cotton into a 250-ml volumetric flask, dilute with chloroform to volume, and mix. Transfer 5.0 ml of this solution to a beaker, and evaporate just to dryness. Transfer the residue to a 100-ml volumetric flask with the aid of, first, 5 ml of alcohol, and then pH 9.6 alkaline borate buffer. Dilute with the buffer to volume, and mix.

Procedure—Concomitantly determine the absorbances of the *Standard preparation* and the *Assay preparation* in 1-cm cells at the wavelength of maximum absorbance at about 241 nm, with a suitable spectrophotometer, using a 1 in 20 solution of alcohol in pH 9.6 alkaline borate buffer as the blank. Calculate the quantity, in mg, of $C_{11}H_{16}N_2O_3$ in the portion of the Tablets taken by the formula: $5C(A_U/A_S)$, in which C is the concentration, in µg per ml, of USP Talbutal RS in the *Standard preparation*, and A_U and A_S are the absorbances of the *Assay preparation* and the *Standard preparation*, respectively.

Talc

» Talc is a native, hydrous magnesium silicate, sometimes containing a small proportion of aluminum silicate.

Packaging and storage—Preserve in well-closed containers.

Identification—Mix 500 mg with about 200 mg of anhydrous sodium carbonate and 2 g of anhydrous potassium carbonate, and heat the mixture in a platinum crucible until fusion is complete. Cool, and transfer the fused mixture to a dish or beaker with the aid of about 50 ml of hot water. Add hydrochloric acid to the liquid until effervescence ceases, then add 10 ml more of the acid, and evaporate the mixture on a steam bath to dryness. Cool, add 20 ml of water, boil, and filter the mixture: an insoluble residue of silica remains. Dissolve in the filtrate about 2 g of ammonium chloride, and add 5 ml of 6 *N* ammonium hydroxide. Filter if necessary, and add sodium phosphate TS to the filtrate: a white, crystalline precipitate of magnesium ammonium phosphate separates.

Loss on ignition—Weigh accurately about 1 g, and ignite at red heat to constant weight: it loses not more than 5.0% of its weight.

Acid-soluble substances—Digest 1.00 g with 20 ml of 3 *N* hydrochloric acid at 50° for 15 minutes, add water to restore the original volume, mix, and filter. To 10 ml of the filtrate add 1 ml of 2 *N* sulfuric acid, evaporate to dryness, and ignite to constant weight: the weight of the residue does not exceed 10 mg (2.0%).

Reaction and soluble substances—Boil 10 g with 50 ml of water for 30 minutes, adding water from time to time to maintain approximately the original volume, and filter. The filtrate is neutral to litmus paper. Evaporate one-half of the filtrate to dryness, and dry at 105° for 1 hour: the weight of the residue does not exceed 5 mg (0.1%).

Water-soluble iron—Slightly acidify with hydrochloric acid the remaining half of the filtrate obtained in the test for *Reaction and soluble substances*, and add 1 ml of potassium ferrocyanide TS: the liquid does not acquire a blue color.

Adhesive Tape

» Adhesive Tape consists of fabric and/or film evenly coated on one side with a pressure-sensitive, adhesive mixture. Its length is not less than 98.0 percent of that declared on the label, and its average width is not less than 95.0 percent of the declared width. If Adhesive Tape has been rendered sterile, it is protected from contamination by appropriate packaging.

Packaging and storage—Preserve in well-closed containers, and