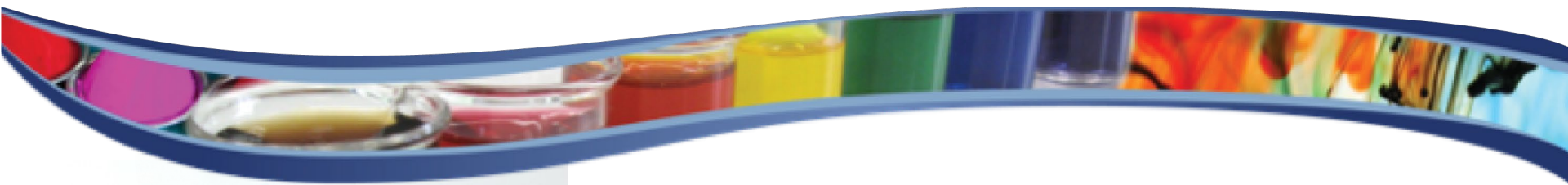


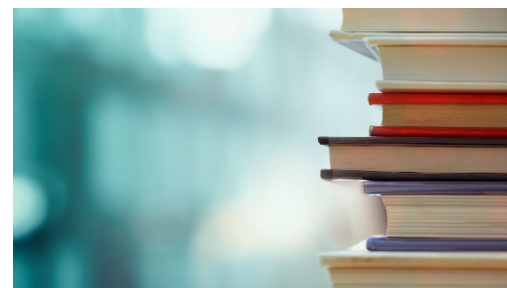
FDA Drug Topics: An Overview of Color Additives in Drug Products - Regulation and Enforcement



Bhakti Petigara Harp, Ph.D.
Office of Cosmetics and Colors
Center for Food Safety and Applied Nutrition
Food and Drug Administration

Learning Objectives

- Describe a color additive
- Identify certification exempt color additives and certified color additives
- Explain certification process for color additives
- Outline the color additive petition process
- Review labeling requirements
- Discuss enforcement tools



Definition of Color Additive

- A color additive is a substance that imparts color to a food, drug, cosmetic, or medical device or to the human body
- FDA must pre-approve the color additives used in FDA-regulated products



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Ideal Properties of Color Additives

- Non-toxic and no physiological activity
- High coloring power so only small quantity needed
- Stable
 - Not light sensitive
 - Not temperature sensitive
 - pH stable
- Free from taste or odor
- Water or oil (solvent) soluble depending on formulation



Purposes of Drug Coloring

- Drug recognition
 - Different colors for different pills
- Branding
 - Purple pills 
 - Blue pills 
- Psychological effects
 - Calm blue for good night's sleep
 - Bright red for speedy recovery
- Brighter colors for children's medicines
- Uniform colors for standard preparations
 - Natural calamine - colored with red iron oxide
 - Lactose used as excipient – colored with caramel
- Opacity for light-sensitive products
 - Keeps active ingredients stable
 - e.g., iron oxides, titanium dioxide, aluminum lakes



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Drug Products That May Have Coloring

- Tablets
 - Inner core
 - Outer coating
- Hard or soft gelatin capsules
 - Outer shell
 - Coated beads
- Branding inks
- Oral liquids
- Topical creams
- Toothpastes, mouthwash
- Ointments



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Types of Color Additives

- Dyes and pigments
- Lakes – insoluble pigments formed from water-soluble dyes, precipitants, and substrata
- Inorganic and mineral compounds
- Plant and animal sources
- Mixtures – color additives made by mixing color additives with diluents
 - Diluents facilitate the use of mixtures in products
 - Listed for drug use under 21 CFR 73.1001
 - Injected drugs
 - Branding inks
 - Externally applied drugs

Certified Color Additives

- “FD&C” and “D&C” color additives
- Synthetic organic dyes and pigments
 - “Synthetic” means man-made
 - “Organic” means made of carbon, hydrogen, nitrogen, oxygen, and sulfur
- Not much dye needed to achieve desired coloring
 - Dyes have high absorptivity values
- Required to be batch certified by FDA
 - Assures conformity to purity requirements
 - Strict limitations for lead, arsenic, and mercury (ppm levels)

Lakes

- Lakes – insoluble pigments formed from water-soluble straight colors, precipitants, and substrata
- Substrata – alumina, aluminum benzoate, barium sulfate, calcium carbonate, kaolin (clay), rosin, talc, titanium dioxide, and zinc oxide
- Precipitants – aluminum (3+), barium (2+), calcium (2+), potassium (1+), sodium (1+), strontium (2+), and zirconium (2+)

Certification-Exempt Color Additives



- Non-“FD&C” color additives
 - Must conform to purity requirements
 - Strict limitations for lead, arsenic, and mercury
 - Manufacturers are responsible for compliance with CFR specifications
- Generally derived from plant, animal or
 - One insect source
 - One cyanobacterium source
- Inorganic or organic compounds
 - May be synthesized or chemically processed
- Compared to certified color additives
 - Have less coloring power
 - Relatively large amounts may be needed to achieve desired coloring
 - Some are less stable and more variable in shade
 - Can vary in composition from batch to batch



FDA's Color Certification Program

- FDA's oldest user fee program
 - Result of 1938 Federal Food, Drug, and Cosmetic Act
- Manufacturers submit samples from each new batch
 - OCAC's Color Certification Branch conducts analyses
 - Certificate and lot number issued if all specifications are met
 - 5-day turnaround
- Continual updating
 - Methodology
 - Instrumentation
- Web-based system
 - Certification database
 - Online certification requests
 - Electronic certification results
- Nomenclature changes upon certification



Common Names for Certified Color Additives



Common name:

- Allura Red AC
- Brilliant Blue FCF
- Erythrosine
- Fast Green FCF
- Indigotine
- Sunset Yellow FCF
- Tartrazine

Certified as:

- FD&C Red No. 40
- FD&C Blue No. 1
- FD&C Red No. 3
- FD&C Green No. 3
- FD&C Blue No. 2
- FD&C Yellow No. 6
- FD&C Yellow No. 5

Certification Analyses

- Total color
 - Spectrophotometry
 - TiCl_3 titration
 - Gravimetric analysis
- Volatile matter
- Insoluble matter
- Extractable matter
- Salts (NaCl , Na_2SO_4)
- Intermediates
- Subsidiary colors
- Reaction by-products
- Unsulfonated aromatic amines
- Polynuclear aromatic hydrocarbons
- Heavy metals
 - Lead, arsenic, mercury
 - Manganese, chromium



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Where to Obtain Certified Color Additives



"Companies Requesting Color Certification Within the Last Two Years" at <https://www.fda.gov/industry/color-certification/companies-requesting-color-certification-within-last-two-years>

How Does a Color Additive Become Listed?



Color Additive Requirements in Federal Food, Drug, and Cosmetic Act (FD&C Act)

- Section 721(a) – Color additives are deemed unsafe unless they are listed in the Code of Federal Regulations
- Section 721(b) – New color additives or new uses for color additives must undergo FDA’s petition review process in order to be listed

Safety Standard for Color Additives



- Not defined in the FD&C Act
- Defined in the legislative history of the 1960 Amendments to the FD&C Act
 - Codified in 21 CFR 70.3(i)
- Safe for a color additive means “reasonable certainty of no harm” from the proposed use

How Does a Color Additive Get FDA Approval?



- Firm submits color additive petition to FDA
- Firm must provide information on:
 - Chemical description and uses
 - Exposure estimate
 - Toxicology studies
 - Environmental assessment
- Qualified FDA scientific experts review data
- If the color additive is shown to be safe, it is listed with its specifications, uses, and restrictions

Information and Scientific Data

Required in a Color Additive Petition

- Identity of proposed color additive
- Physical, chemical, and biological properties
- Proposed chemical specifications
- Manufacturing process description
- Stability data
- Intended uses and restrictions
- Proposed labeling
- Tolerances and other limitations
- Analytical methods for enforcing chemical specifications
- Analytical methods for determining color additive in products
- Safety studies
- Estimate of probable exposure
- Proposed regulation
- Proposed exemption from batch certification
- Environmental assessment or claim for categorical exclusion

Chemistry Review of a Color Additive Petition



- Guidance for Industry: Color Additive Petitions - FDA Recommendations for Submission of Chemical and Technological Data on Color Additives for Food, Drugs, Cosmetics, or Medical Devices
- <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-color-additive-petitions-fda-recommendations-submission-chemical-and-technological>

Should a New Color Additive Be Batch Certified?



- Petition must show why certification is not necessary for the protection of public health
 - Certification needed for color additives likely to contain toxic impurities
- All certifiable and non-certifiable color additives must meet FDA's specifications

Estimate of Probable Exposure to a Color Additive



- Calculation of estimated daily intake (EDI) or dermal exposure
- For establishing uses, restrictions, specifications
- Exposure estimate used in safety review



Review of Safety Studies

- Guidance for Industry and Other Stakeholders: Redbook 2000
- Used to evaluate toxicity studies
- <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-and-other-stakeholders-redbook-2000>

Environmental Assessment (21 CFR Part 25)



- Guidance for Industry: Preparing a Claim of Categorical Exclusion or an Environmental Assessment for Submission to CFSAN
- Categorical exclusions
 - 21 CFR sections 25.30 and 25.32
- <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-preparing-claim-categorical-exclusion-or-environmental-assessment-submission-cfsan>

Color Additive Regulations

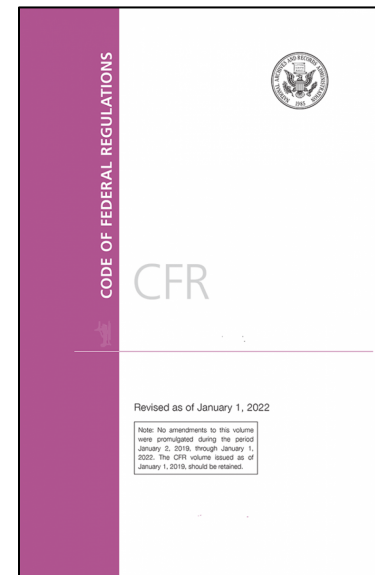
- Color additive listing regulations
 - 21 CFR Part 73 (thirty allowed in drugs)
 - Non-“FD&C” color additives
 - Exempt from certification
 - 21 CFR Part 74 (thirty-six allowed in drugs)
 - “FD&C,” “D&C,” and “Ext. D&C” color additives
 - Required to be certified
 - 21 CFR Part 82
 - Most color additive lakes
 - Required to be certified

- Additional color additive requirements
 - 21 CFR 70.5 (general restrictions)
 - Eye area use, injections, sutures (none permitted for injections)
 - 21 CFR Parts 70, 71, 80
 - Definitions, petition provisions, certification provisions

Color Additive Listing Regulation



- Identity
- Specifications
- Uses and restrictions
- Labeling
- Exemption from certification *or*
- Requirement for certification





Permitted Uses for Color Additives in Drugs

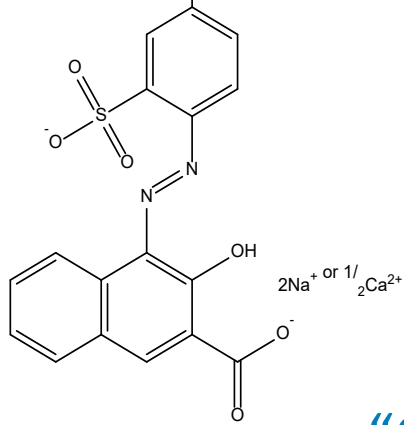
- General use
 - Ingested drugs
- External use
 - Topically applied drugs
- Specific products
 - Mouthwashes and dentifrices
- Eye area use
 - Must be specifically authorized



21 CFR Part 74 Certified Color Additives for Use in Drugs

- FD&C Blue No. 1
- FD&C Green No. 3
- FD&C Red No. 3
- FD&C Red No. 40
- FD&C Yellow No. 5
- FD&C Yellow No. 6
- D&C Blue No. 4
- D&C Green No. 5
- D&C Orange No. 4
- D&C Red No. 7
- D&C Red No. 22
- D&C Yellow No. 10

21 CFR 74.1307 D&C Red No. 7



“Coal tar” dye (made synthetically)

Batch certified because likely to contain toxic impurities

Identity. The color additive D&C Red No. 7 is principally the calcium salt of 3-hydroxy-4-[(4-methyl-2-sulphophenyl)azo]-2-naphthalenecarboxylic acid (CAS Reg. No. 5281-04-9)

D&C Red No. 7 is an “azo” pigment

It is manufactured by diazotizing 2-amino-5-methylbenzenesulfonic acid and coupling with 3-hydroxy-2-naphthalenecarboxylic acid in the presence of calcium chloride

Chemical Specifications for D&C Red No. 7



- Sum of volatile matter (at 135 °C) and chlorides and sulfates (calculated as sodium salts), not more than 10%
- 1-[(4-Methylphenyl)azo]-2-naphthalenol, not more than 0.015%
- 2-Amino-5-methylbenzenesulfonic acid, calcium salt, not more than 0.2%
- 3-Hydroxy-2-naphthalenecarboxylic acid, calcium salt, not more than 0.4%
- 3-Hydroxy-4-[(4-methylphenyl)azo]-2-naphthalene-carboxylic acid, calcium salt, not more than 0.5%.
- p-Toluidine, not more than 15 ppm
- Lead, not more than 20 ppm
- Arsenic, not more than 3 ppm
- Mercury, not more than 1 ppm
- Total color, not less than 90%

Uses and Restrictions for D&C Red No. 7



- May be used for coloring drugs such that the combined total of D&C Red No. 6 and D&C Red No. 7 does not exceed 5 milligrams per daily dose of the drug



FD&C Lakes

- Straight color components permitted in drugs
 - FD&C Blue No. 1
 - FD&C Blue No. 2
 - FD&C Green No. 3
 - FD&C Red No. 40
 - FD&C Yellow No. 5
 - FD&C Yellow No. 6
- Must be made with alumina and aluminum (3+)
- Permitted in drugs for eye area use
 - FD&C Blue No. 1 aluminum lake
 - FD&C Red No. 40 aluminum lake
 - FD&C Yellow No. 5 aluminum lake
- Straight colors required to be certified prior to use in lakes
- Finished FD&C lakes required to be certified

D&C Lakes

- Most D&C straight colors are not required to be certified in order to be used in lakes
 - e.g., D&C Red No. 28, D&C Yellow No. 10
- *Except:* Two D&C straight colors are required to be certified prior to use in lakes
 - D&C Red No. 33
 - D&C Red No. 36
- Finished D&C lakes required to be certified

21 CFR Part 73 Color Additives Exempt from Certification for Use in Drugs



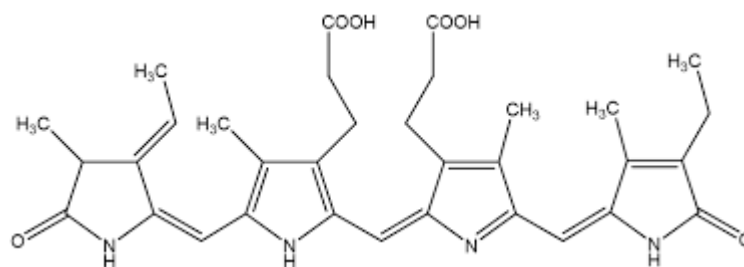
- Plant sources
 - Annatto extract
 - Canthaxanthin
 - β -Carotene
 - Potassium sodium copper chlorophyllin
- Animal source
 - Cochineal extract and carmine
- Inorganic compounds
 - Alumina (dried aluminum hydroxide)
 - Mica-based pearlescent pigments
 - Synthetic iron oxide
 - Titanium dioxide
 - Zinc oxide
- Others
 - Caramel
 - Spirulina extract

21 CFR 73.1530 Spirulina Extract – New Color Additive for Use in Drugs



Identity.

Spirulina extract is prepared by the filtered aqueous extraction of the dried biomass of *Arthrospira platensis*. The color additive contains phycocyanins as the principal coloring components.



phycocyanobilin chromophore

Chemical Specifications and Uses for Spirulina Extract



- Lead, not more than 2 ppm
- Arsenic, not more than 2 ppm
- Mercury, not more than 1 ppm
- Negative for microcystin toxins

- May be used for coloring coating formulations applied to drug tablets and capsules, at levels consistent with good manufacturing practice



Labeling Requirements



Color Additive Labeling for Prescription Drugs



- Section 502(e) of the FD&C Act
 - Color additives in prescription drugs must be declared by their established (listed) names
 - e.g., D&C Yellow No. 10
- *Except* 21 CFR 201.100(b)(5)
 - Most color additives in non-oral prescription drugs can be called “coloring” unless required by another regulation
 - FD&C Yellow No. 5 and FD&C Yellow No. 6 must be declared by their listed names (21 CFR 201.20(c))

Additional Color Additive Labeling Requirement for FD&C Yellow No. 5



- 21 CFR 201.20(a)
- FD&C Yellow No. 5 must be labeled on all drugs
 - “Contains FD&C Yellow No. 5 (tartrazine) as a color additive” or “Contains color additives including FD&C Yellow No. 5 (tartrazine)”
- 21 CFR 74.1705 and 21 CFR 201.20(b)
- All prescription drug products containing FD&C Yellow No. 5 are also required to be labeled with a warning statement about possible allergic reactions
 - “This product contains FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons.”

*Each tablet contains rosuvastatin calcium equivalent to 5 mg of rosuvastatin.

USUAL DOSAGE:

See accompanying Prescribing information.

WARNING:

Contains FD&C Yellow No. 5 (tartrazine) as a color additive.

As with all medications, keep out of the reach of children

Store at controlled room temperature, 20-25°C (68-77°F) [see USP Controlled Room Temperature].

Protect from moisture.

M.L.No.: 5/MN/TS/2014/F/G

Issued: 01/2017



Under precautions:
This product contains FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons

Tablets

5 mg*



Rx Only

1000 Tablets

Batch:

Expiry:

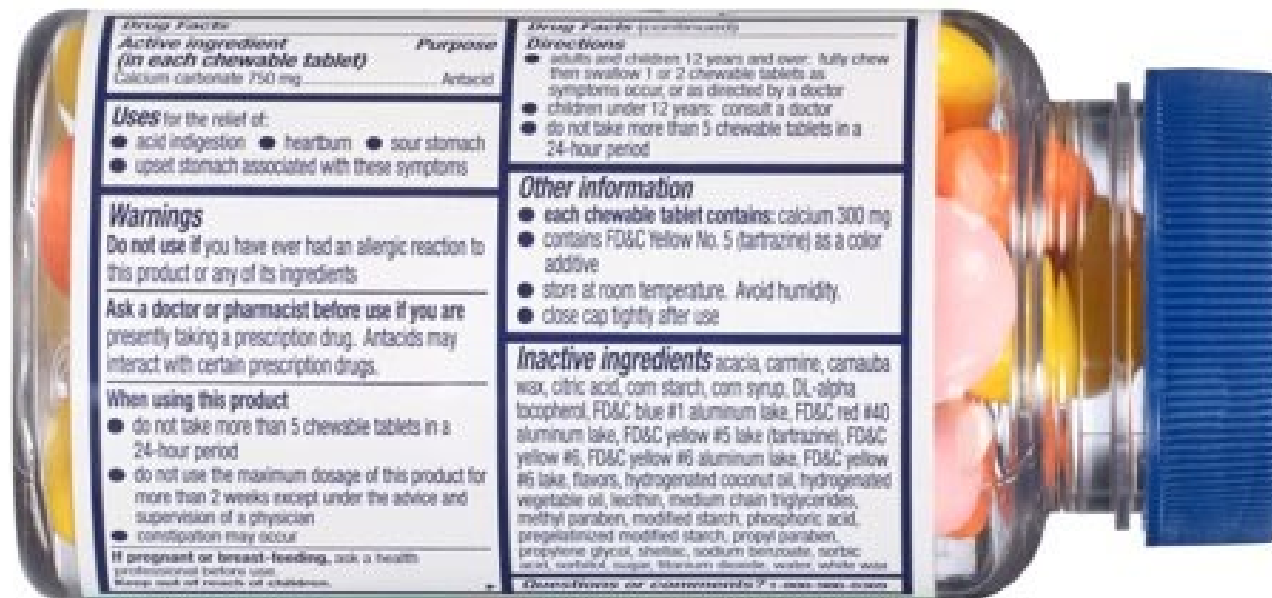
Blank area for Batch and Expiry information.

Color Additive Labeling for Over-The-Counter Drugs



- Section 502(e) of the FD&C Act
 - Color additives in over-the-counter drugs must be declared by their established (listed) names
- 21 CFR 201.66(c)(8) contains the inactive ingredient requirements
- 21 CFR 201.66(d) contains the Drug Facts labeling formats
 - Color additives must be declared in the “Inactive ingredients” section of the Drug Facts label

<p>Drug Facts</p> <p>Active ingredient (in each tablet) Esomeprazole 20 mg (Each delayed-release tablet corresponds to 22.3 mg esomeprazole magnesium trihydrate)</p> <p>Purpose Acid reducer</p>	<p>Drug Facts (continued)</p> <p>If pregnant or breast-feeding, ask a health professional before use. Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.</p>
<p>Uses</p> <ul style="list-style-type: none"> ■ treats frequent heartburn (occurs 2 or more days a week) ■ not intended for immediate relief of heartburn; this drug may take 1 to 4 days for full effect. 	<p>Directions</p> <ul style="list-style-type: none"> ■ adults 18 years of age and older ■ this product is to be used once a day (every 24 hours), every day for 14 days ■ may take 1 to 4 days for full effect <p>14-Day Course of Treatment</p> <ul style="list-style-type: none"> ■ swallow 1 tablet with a glass of water before eating in the morning ■ take every day for 14 days ■ do not take more than 1 tablet a day ■ swallow whole. Do not crush or chew tablets. ■ do not use for more than 14 days unless directed by your doctor <p>Repeated 14-Day Courses (if needed)</p> <ul style="list-style-type: none"> ■ you may repeat a 14-day course every 4 months ■ do not take for more than 14 days or more often than every 4 months unless directed by a doctor <p>■ children under 18 years of age: ask a doctor before use. Heartburn in children may sometimes be caused by a serious condition.</p>
<p>Warnings</p> <p>Allergy alert: Do not use if you are allergic to esomeprazole.</p> <p>Do not use if you have:</p> <ul style="list-style-type: none"> ■ trouble or pain swallowing food, vomiting with blood, or bloody or black stools ■ heartburn with lightheadedness, sweating or dizziness ■ chest pain or shoulder pain with shortness of breath; sweating; pain spreading to arms, neck or shoulders; or lightheadedness ■ frequent chest pain <p>These may be signs of a serious condition. See your doctor.</p>	<p>Other Information</p> <ul style="list-style-type: none"> ■ read the directions and warnings before use ■ keep out of reach of children. It contains important information. ■ store at 20-25°C (68-77°F)
<p>Ask a doctor before use if you have</p> <ul style="list-style-type: none"> ■ had heartburn over 3 months. This may be a sign of a more serious condition. ■ frequent wheezing, particularly with heartburn ■ unexplained weight loss ■ nausea or vomiting ■ stomach pain <p>Ask a doctor or pharmacist before use if you are taking</p> <ul style="list-style-type: none"> ■ warfarin, clopidogrel or clobazam (blood-thinning medicines) ■ prescription antifungal or anti-yeast medicines ■ digoxin (heart medicine) ■ diazepam (anxiety medicine) ■ tacrolimus or mycophenolate mofetil (immune system medicines) ■ prescription antiretrovirals (medicines for HIV infection) ■ methotrexate (arthritis medicine) 	<p>Inactive ingredients</p> <p>corn starch, croscopolidone, D&C red no. 27 aluminum lake, FD&C blue no. 2 aluminum lake, FD&C red no. 40 aluminum lake, glyceryl monostearate, hydroxypropyl cellulose, hypromellose, magnesium stearate, methacrylic acid copolymer, mica, microcrystalline cellulose, paraffin, polyethylene glycol, polyethylene glycol succinate, sodium stearyl fumarate, sucrose, talc, titanium dioxide, triethyl citrate</p>
<p>Stop use and ask a doctor if</p> <ul style="list-style-type: none"> ■ your heartburn continues or worsens ■ you need to take this product for more than 14 days ■ you need to take more than 1 course of treatment every 4 months ■ you get diarrhea 	<p>Questions or comments? call toll free 1-866-226-1600, 9 AM to 5 PM EST</p>



Enforcement of Color Additive Requirements



Common Color Additive Violations

- Adulteration
 - Uncertified material used in a product
 - Non-permitted color additives used in a product
- Misbranding
 - Added color on ingredient label but not on finished product label



FDA's Enforcement of Drug Color Additive Requirements

- Authorized by FD&C Act and other applicable laws
 - 801(a)(3)
- Adulteration provisions - 501(a)(4)
- Misbranding provisions - 502(e and m)
- Import alerts
- Screening criteria for particular firms/products

Enforcement Tools for Color Additive Violations in Foods, Drugs, and Cosmetics



- Recalls
- Warning and untitled letters
- Detention, detention without physical examination (DWPE), import alerts
- Seizures
- Injunctions
- Prosecutions
- Civil money penalties

FDA's Enforcement of Drug Color Additive Requirements



- A drug may fail to comply with CGMP requirements for
 - Uncertified color additives
 - Non-permitted color additives
- Possible actions
 - Firm issued a warning letter *or*
 - Product and firm placed on import alert
 - IA 66-40 Detention Without Physical Examination of Drugs From Firms Which Have Not Met Drug GMPs
 - IA 66-41 Detention Without Physical Examination of Unapproved New Drugs Promoted In The U.S.

Submitting Adverse Event Reports to FDA

FDA



MedWatch Online Voluntary Reporting Form



Welcome

Health professionals, consumers and patients can voluntarily report observed or suspected adverse events for human medical products to FDA. Voluntary reporting can help FDA identify unknown risk for approved medical products. Reporting can be done through our online reporting portal or by downloading, completing and then submitting FDA Form 3500 (Health Professional) or 3500B (Consumer/Patient) to MedWatch: The FDA Safety Information and Adverse Event Reporting Program.

Begin Online Report



**En español para el
consumidor / paciente**
(formulario 3500B de la FDA)



Click here to continue filling out an incomplete report. You will need Report ID and Report Date. You will have 3 days to complete this report from the

- How to Report:
 - Online (www.fda.gov/medwatch)
 - Download the form
 - Mail
 - Fax 1-800-332-0178
- For questions about the form:
 - 1-800-332-1088

U.S. Food and Drug Administration. MedWatch: The FDA Safety Information and Adverse Event Reporting Program. Available at: <https://www.fda.gov/Safety/MedWatch/default.htm>

Summary:

Important Color Additive Requirements



- Only approved and listed color additives may be used in foods, drugs, cosmetics, and medical devices marketed in the U.S.
- All color additives must comply with the requirements in their listing regulations
 - Including purity requirements
- Color additives must be used appropriately
 - Manufacturers must consult the listing and labeling regulations
- Certified material must be used in products when required



Resources for Color Additives

- Summary of Color Additives for Use in United States in Foods, Drugs, Cosmetics, and Medical Devices:
<http://www.fda.gov/ForIndustry/ColorAdditives/ColorAdditiveInventories/ucm115641.htm>
- Code of Federal Regulations : eCFR :: 21 CFR Part 74 Subpart B – Drugs:
<https://www.ecfr.gov/current/title-21/chapter-I/subchapter-A/part-74#subpart-B>
- Color Additives: <https://www.fda.gov/industry/color-additives>
- Color Additive Laws, Regulations, and Guidance: <https://www.fda.gov/industry/color-additives/color-additive-laws-regulations-and-guidance>
- Color Additives in Specific Products: <https://www.fda.gov/industry/color-additives/color-additives-specific-products>
- Color Additive Science and Research: <https://www.fda.gov/industry/color-additives/color-additive-science-and-research>

- Questions to druginfo@fda.hhs.gov

Thank you for your attention!

