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Review Article

Coloring Agents: Current Regulatory Perspective for Coloring Agents Intended for Pharmaceutical & Cosmetic Use

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Abstract:
Coloring agents are indispensable requirement of any pharmaceutical dosage form. It is used for varied purpose extending from aesthetic to technical advantage. These are potent in nature and small concentrations are sufficient in order to establish their said purpose. These concentrations if not maintained within prescribed limit, these can lead to serious toxicity and this is especially endangering to geriatric and pediatric populations. These limits are generally established after thorough preclinical trials which include testing on animals, human volunteers. Therefore, it is utmost necessity to use these colors in pharmaceutical dosage form cautiously with correct reasoning and rationale for its use in particular dosage form. Current review article mentions about the evolution of regulations for these colors, current recommended colors and its concentrations wherever provided. In order to bring about harmonization with respect to manufacturing of drugs and dosage forms, it is critical to be well aware about the regulatory principles existing over the world. Regulatory classification and definitions for colors in pharmaceutical use from US (US FDA Regulation: 21 CFR part), EU (EU commission), India (FDA, D&C cosmetic act 1940) are described. Considering serious health hazards from persistent use of these coloring agents above recommended concentrations, it is vital to understand the regulatory aspects and apply it fruitfully during formulation of any dosage form. This will ensure the provision of good health care for all the diseased populations across the world.

Key words: Coloring agents, 21 CFR, EU commission, D&C cosmetic act, regulatory, straight color, lakes, dyes, pigment.

1. INTRODUCTION

Coloring agents are most commonly employed in almost all the kinds of pharmaceutical dosage forms. The rationale behind use of coloring agents can be technical or for aesthetic purpose. A color additive, as defined by US FDA regulation, is any dye, pigment, or other substance that can impart color to a food, drug, or cosmetic or to the human body. Color additives are important components of many products, making them attractive, appealing, appetizing, and informative. Added color serves as a kind of code that allows us to identify products on sight, like candy flavors, medicine dosages, and left or right contact lenses. Although it is used in small concentrations in many dosage forms, its safety is not much discussed. Therefore, it is utmost need to understand the safe concentrations and impact of these coloring agents on biological systems. The present study aimed at creating awareness with respect to regulations followed worldwide for coloring agents. It is utmost important to understand these regulations and to follow judiciously as there many coloring agents which are mentioned selectively for the pharmaceutical use. This review is synchronization of regulatory requirements of coloring agents from US, EU, and Indian FDA. Also, few examples are cited where color manufacturer's are queried due to their non compliance to the regulations and hence researcher also need to have this technical understanding for selection of color and source.

2. HISTORICAL PERSPECTIVES: THE BASIS FOR CURRENT REGULATIONS

Naturally occurring color additives from vegetable and mineral sources were used to color foods, drugs, and cosmetics in ancient times. Paprika, turmeric, saffron, iron and lead oxides, and copper sulfate are some examples. In 1856, William Henry Perkin discovered the first synthetic organic dye, called mauve. Dyes were first produced from by-products of coal processing, they were known as "coal-tar colors." In 1881, the U.S. Department of Agriculture's (USDA) Bureau of Chemistry began research on the use of colors in food.

Butter and cheese were the first foods for the use of artificial coloring agents. By 1900, many foods, drugs, and cosmetics available in the U.S. were artificially colored[1]. However, not all of the coloring agents were harmless and some were being used to hide inferior or defective foods.

A careful assessment of the chemicals used for coloring foods at times found many blatantly poisonous materials such as lead, arsenic, and mercury being added.

In many cases, the toxicities of the starting materials for synthesizing coloring agents were well known and could be toxins, irritants, sensitizers, or carcinogens. Therefore, in 1906, Congress passed the Food and Drugs Act, which prohibited the use of poisonous or deleterious colors in confectionery and the coloring or staining of food to conceal damage or inferiority. Further this act was improvised and regulations were made stricter with respect to food colors and finally this lead to the listing of new colors; and made mandatory for the previously voluntary certification program for batches of listed colors. Color additive lakes were in use by this time and were included in the provisions of the 1938 FD&C Act. Further response to the 1938 Act, through public hearings, FDA created the FD&C, D&C, and Ext. D&C nomenclature for certifiable color additives. FDA also established labeling and recordkeeping provisions, identified diluents that could be added to color additives, and established procedures for requesting certification of color additives and adding new color additives to the permitted list.

However, in 1950, with approved listed color also, serious toxicities were reported especially with pediatric population (children became ill from eating an orange Halloween candy containing 1-2% FD&C Orange No. 1,) which lead to amendment of this act and lead to generation of CFR (Code of federal Regulations) for color and color additives which is commonly practiced and mandatory to be followed by all the manufacturer's using color or color additive in foods, drugs, cosmetics.

The Food and Drug Administration (FDA) have reported of toxicity, including death, temporally associated with the use of FD&C Blue No. 1 (Blue 1) in enteral feeding solutions where Blue 1 was intended to help in the detection and/or monitoring of pulmonary aspiration in patients being fed by an enteral feeding tube[2].

3. CURRENT REGULATION OF COLOR ADDITIVES AS PROVIDED BY US FDA

US FDA has established regulations for color additives in Title 21 of the CFR, parts 70-82. Out of the parts 70-82, parts 73,74 and 82 have provided list of color additives, its chemical specifications, its intended use, its restrictions i.e. dosage forms where it is restricted for its use as color additive, its labeling requirement and whether it needs to be certified color. The regulations in 21 CFR part 71 describe the premarket approval process required for new color additives and new uses for listed color additives, if applicable. 21 CFR part 80 describes the actual stepwise procedure to be followed for the certification of color additive. Additional regulations that provide specific requirements for color additives in foods, drugs, cosmetics, and medical devices are found in other parts of the CFR. For example, the labeling of food products is found at 21 CFR 101.22(k) and cosmetic products at 21 CFR 701.3. Color additives are sometimes called "artificial color" or "artificial coloring" (21 CFR 101.22(a)(4)). From the regulatory standpoint, the term "colorant" refers to a dye or pigment used in a food contact material such as a polymer and doesn't migrate to food. These materials are regulated not as color additives but as food additives (21 CFR 178.3297(a))[2].

These parts of CFR related to color additives can be summarized in below table 1:

Table 1: List of CFR parts related to color additives.

CFR PART	Details about color additives
PART 70	It provides the definition, general provisions, packaging & labeling instructions and safety evaluation criteria's for each color additive.
PART 71	It explains the administrative procedure to be followed for filing of petitions for color additives.
PART 73	It provides the list of color additives which are exempt from certification procedure and can be used directly for foods, drugs, cosmetics and medical devices.
PART 74	It provides the list of color additives which require certification procedure for use in foods, drugs, cosmetics and medical devices.
PART 80	It provides procedure to be followed for certification of color additive for the list of color additives that are listed under part 74.
PART 81	It provides general specifications and general restrictions for provisionally listed color additives for use in foods, drugs and cosmetics. Provisionally listed color additives are ones that are allowed for use before certification procedure.
PART 82	It provides the list of certified provisionally listed colors and its specifications.

4. CLASSIFICATION OF COLOR ADDITIVES

As per 21 CFR, color additives are classified as:

4.1 Certifiable colors

These color additives are derived primarily from petroleum and are sometimes known as "coal-tar dyes" or "synthetic-organic" colors. Today, most of this category colors are made from petroleum.

Except in the case of coal-tar hair dyes, these colors are not permitted to be used in drugs and cosmetics unless it is certified by FDA. FDA certified means that the batch of color intended to be used in end product has passed analysis test for its composition and purity in FDA's own laboratories or FDA approved laboratories. However, if the batch is not certified by FDA then it cannot be used[3].

These certified colors generally have three-part names. The names include a prefix FD&C, D&C, or External D&C; a color; and a number. For an example; "FD&C Yellow No. 5." Certified colors also may be identified in cosmetic ingredient declarations by color and number alone, without a prefix (such as "Yellow 5").

Procedure for certification[4]:

As per CFR, title 21, part 80 describes about color additive certification. It compromises of two parts: subpart A and subpart B. Subpart A gives general provisions and Subpart B explains about the certification procedure.

Subpart B has further subclasses under part 80 and these are listed as below:

Table 2: Subclasses of CFR, title 21, part 80

Subclasses of part 80	Title	Description
80.21	Requests for Certification	This covers the details and form which is to be filled by color manufacturers' and it is to be submitted to US FDA commissioner of food and drugs regarding quantity of sample of color additive, storage condition, container used for the same, chemical base used for the color etc.
80.22	Samples to accompany requests for certification.	Describes the content to be of representative sample with complete labeling details for color to be certified.
80.31	Certification	Conditions under which color may get certified or may be disqualified by commissioner.
80.32	Limitations of certificates.	All the conditions under which certificate can be denied.
80.34	Authority to refuse certification service	Explains the denial of certification when inventory records and details of intermediates used for making color additive is not fulfilled as per US FDA regulations.
80.35	Color additive mixtures: certification and exemption from certification	This refers to mixtures as per US FDA which can be certified and which are exempted from certification and list of diluents for mixtures of color additives.
80.37	Treatment of batch pending certification.	The procedure on holding of the batch of color additive which is under certification procedure.
80.38	Treatment of batch after certification.	Storage of batch after color certification and labeling with certified lot number.
80.39	Records of distribution.	Maintenance of records of batch certified by manufacturer.

4.2 Colors exempt from certification

These color additives are obtained primarily from natural sources such as from mineral, plant, or animal origin. They are not required to be subjected to batch certification requirements. However, they are still considered as artificial colors, and when used in cosmetics or other FDA-regulated products, they must comply with the identity, specifications, uses, restrictions, and labeling requirements stated in the regulations [21 CFR 73].

4.3 Straight color

"Straight color" refers to any color additive listed in 21 CFR 73, 74, and 81 [21 CFR 70.3(j)]. 21 CFR part 73 enlists the name of the color, its chemical name, intended use and restricted use[5]. Few of the colors from the list of 21 CFR part are as given in below table 3:

Table 3: List of color additives under term of " Straight color " as per 21 CFR

S. No.	21 CFR Part/ sub part number	COLOR ADDITIVE	USES AND RESTRICTIONS
01	73.1015	Chromium-Cobalt-Aluminum Oxide (Blue green pigment)	For coloring linear polyethylene surgical sutures for use in general surgery.
02	73.3115	2-[[2,5-Diethoxy-4-[(4-methylphenyl)thiol] phenyl]azo]-1,3,5-benzenetriol (common name not available).	May be used to mark soft (hydrophilic) contact lenses with r or l for right and left identification.
03	73.1025	Ferric Ammonium Citrate	May be used in combination with pyro-(green or brown)gallol, as listed in 73.1375, for coloring plain or chromic catgut sutures for use in general and ophthalmic surgery.
04	73.3106	C.I. Reactive Blue 246 Chemical name: 1,4-bis[4-[(2-methacryl-oxyethyl)phenylamino] anthraquinone.	Contact lenses
05	74.1109	D&C Blue No. 9	For coloring cotton and silk surgical sutures, including sutures for ophthalmic use.
06	74.3106	D&C Blue No. 6	Polyethylene terephthalate surgical sutures for general surgical use. Plain or chromic collagen absorbable sutures for ophthalmic surgical use and general surgical use. Polypropylene surgical sutures for general surgical use. Polydioxanone synthetic absorbable sutures for ophthalmic and general surgical use.

4.4 Lake

A lake is a straight color extended on a substratum by adsorption, co-precipitation, or chemical combination that does not include any combination of ingredients made by a simple mixing process [21 CFR 70.3(l)]. Because lakes are not soluble in water, they often are used when it is important to keep a color from "bleeding," as in lipstick. In some cases, special

restrictions apply to their use. Further, approved color additives are also classified for tailored use in foods, drugs & cosmetics are as follows:

A. Color Additives Approved for Use in Human Food
B. Color Additives Approved for Use in Drugs
C. Color Additives Approved for Use in Cosmetics
D. Color Additives Approved for Use in Medical Devices

Few of the colors from each part are listed from the exhaustive list of table from 21 CFR part areprovided in below table 4 (List of colors as per 21 CFR part for use in foods and drugs) and table 5 (List of colors as per 21 CFR part for use in cosmetics and medical devices) below[5]:

Table 4: List of colors as per 21 CFR part for use in food, drugs, cosmetics and medical devices

Color Additives Approved for Use in Human Food (SUB PART A)				**Color Additives Approved for Use in Drugs (SUB PART B)**			
21 CFR part 73 (Color additives exempt from batch certification)		**21 CFR part 74** (Color additives subject to batch certification)		**21 CFR part 73** (Color additives exempt from batch certification)		**21 CFR part 74** (Color additives subject to batch certification)	
Straight Color	**Uses and Restrictions**	**Straight Color**	**Uses and Restrictions**	**Straight Color**	**Uses and Restrictions**	**Straight Color**	**Uses and Restrictions**
Mica-based pearlescent pigments.	Cereals, confections and frostings, gelatin desserts, hard and soft candies(including lozenges), nutritional supplement tablets and gelatin capsules, and chewing gum.	FD&C Blue No. 1	Foods generally.	Caramel	Ingested and topically applied drugs generally	D&C Red No. 21	Drugs generally

Color Additives Approved for Use in Human Food (SUB PART A)				Color Additives Approved for Use in Drugs (SUB PART B)			
21 CFR part 73 (Color additives exempt from batch certification)		**21 CFR part 74** (Color additives subject to batch certification)		**21 CFR part 73** (Color additives exempt from batch certification)		**21 CFR part 74** (Color additives subject to batch certification)	
Straight Color	**Uses and Restrictions**	**Straight Color**	**Uses and Restrictions**	**Straight Color**	**Uses and Restrictions**	**Straight Color**	**Uses and Restrictions**
Riboflavin	Foods generally.	FD&C Blue No. 2	Foods generally.	Synthetic iron oxide	Ingested or topically applied drugsingested dosage by man NTE mg/day (as Fe).	D&C Red No. 31	Externally applied drugs
Canthaxanthin	Foods generally, NTE 30 mg/lb of solid or semisolid food or per pint of liquid food; May also be used in broiler chicken feed.	FD&C Green No. 3	Foods generally.	Zinc oxide	Externally applied drugsincluding eye area use.	D&C Orange No. 5	Externally applied drugs (NTE 5 mg/daily dose of drug).Mouthwashes and dentifrices.

Table 5: List of colors as per 21 CFR part for use in cosmetics and medical devices

Color Additives Approved for Use in Cosmetics **(SUB PART C)**		Color Additives Approved for Use in Medical Devices **(SUB PART D)**	
21 CFR part 73 (Color additives exempt from batch certification)	**21 CFR part 74** (Color additives subject to batch certification)	**21 CFR part 73** (Color additives exempt from batch certification)	**21 CFR part 74** (Color additives subject to batch certification)

Straight Color	Uses and Restrictions	Straight Color	Uses and Restrictions	Straight Color	Uses and Restrictions	Straight Color	Uses and Restrictions
Bismuth citrate	Cosmetics intended for coloring hair on the scalp only NTE 2.0 percent.	D&C Black No. 2	Eyeliner, brush-on-brow, eye shadow, mascara, lipstick, blushers and rouge, makeup and foundation, and nail enamel.			D&C Red No. 17	Contact lenses.
Iron oxides	Cosmetics generallyincluding eye area use.	Ext. D&C Violet No. 2	Externally applied cosmetics.	2-[[2,5-Diethoxy- 4-[(4-methylphenyl)thiol] phenyl] azo] - 1,3,5-benzenetriol	Formed in situ in soft contact lenses to mark L and R NTE 1.1x10-7 g/lens.	D&C Blue No. 6	Various sutures NTE specified levels.
Luminescent zinc sulfide	Nail polish and externally applied facial makeupNTE 10% of final product for limited, occasional use.	D&C Red No. 33	Externally applied cosmetics; mouthwashes, dentifrices; cosmetic lip products (NTE[)] 3% (by wt) of finished cosmetic product).	Logwood extract	For coloring nylon 66, nylon 6, or silk non-absorbable sutures; NTE 1% general and ophthalmic surgery.	FD&C Blue No. 2	Nylon surgical sutures; NTE 1% general surgery.

NTE: Not to exceed.

With respect to the above data in table, following additional information provided in 21 CFR part with respect to color additives. Color additives listed in 21 CFR parts 74 (colors subject to certification) and 82 (certified provisionally listed colors and its specifications) must be analyzed and batch certified by FDA before they can be used in any FDAregulated product marketed in the U.S. This requirement applies to products imported into US as well as those manufactured domestically (US). Manufacturers of certified color additives must include on the label the name of the certified color additive, a statement indicating general use limitations, any quantitative limitations in products, and the certification lot number assigned to the batch.

When it is mentioned that Color additives that are permitted for general use, it means that it may not be used in the area of the eye, in injections, or in surgical sutures unless such use is specified in the color additive listing regulation. Currently no color additives are listed or permitted for use in injected products (such as tattoos or permanent makeup).

When it is mentioned thatColor additives that are permitted for external application, it means that it may not be used in the area of the eye, in injections, or in surgical sutures unless such use is specified in the color additive listing regulation. However, some color additives that are permitted for external application are permitted for use in dosage forms such as mouthwashes, dentifrices, or lipsticks in limited amounts as specified in concentrations as per regulation.

5. REGULATION FOR EXPORT OF CONSUMABLE/UTILITY ITEMS CONTAINING COLORING AGENTS AS LAID BY US FDA

With the exception of most meat and poultry, all food, drugs, biologics, cosmetics, medical devices, and electronic products that emit radiation, as defined in the FD&C and related Acts, are subject to examination by FDA when they are being imported or offered for import into the United States. Most meat and poultry products are regulated by the U.S. Department of Agriculture. With respect to color additives (used in foods, drugs and cosmetics) from manufactured finished drug products that are imported to US, there are import alerts issued by US FDA[6,7]. There are several import alerts, out of which two of them are discussed here. These are listed below as follows:

1. "Detention without Physical Examination and Guidance of Foods Containing Illegal and/or Undeclared Colors." (for foods).
2. "Detention without Physical Examination Of Cosmetics Containing Illegal Colors" . (For cosmetics).

These import alerts are guidance framed by US FDA for their field personnel to follow during the inspection of the manufacturer(s) and products(s) during examination of imported commodities. Few of the examples from each of this guidance are explained in this review article to explain the seriousness of regulations which are required to be followed in US for color additives. For example, there is list of food items which were detained from import in US (in the year: 2009) under this guidance ("Detention without Physical Examination and Guidance of Foods Containing Illegal and/or Undeclared Colors")[8]. The alphabetical list is provided with respect to country's name. One of the Indian company manufacturing food products for US which was detained as per this guidance is "Haldiram Foods International Ltd" for export of food product under name of Cheesy bites, Badam halwa baked snack etc. The identified reason was the use of color FD&C YELLOW #6 (SUNSET YELLOW FCF) which was used in the food product but it was not declared on its label. Another example is detention of cosmetics under the import alert no. 53-06. This alert, which was initially issued in 1985, was based on the detention of make- up kits with eye area cosmetics especially cosmetic products coming to US from Taiwan and containing illegal color additives. In 1993, analysis of an eye color compact collected by New York district revealed the presence of

D&C Red, a delisted synthetic color additive. Further in 1995, shampoos were sampled and analyzed and it was found to contain unsafe/illegal and undeclared colors. The unsafe/illegal colors included non-permitted external D & C Red #10 and Ponceau 4R colors. One of the example of indian firm mentioned in the list of this import alerts include 'Hindustan unilever ltd'. Company was detained in year 2010 for its import of product; 'Pears Soap'; Hamam soap (both fall under category of bath soaps and Detergents for personal cleanliness; 53 J-01). These were detained due to presence of color additive pigment red (C.I. 12490); 5 and phthalocyanine green (C.I. 74260, Pigment Green 7) respectively. Phthalocyanine green is listed for use in medical devices like contact lenses, whereas, pigment red 5 is not listed at all in the list of approved colors[10]. Therefore, these are mentioned in import alert as "no certifiable equivalent – non permitted" against the names of these products[11]. Reader can refer to the exhaustive list which is described country wise in this import alert.

Another example of import alert issued by US FDA is related to hair dye product's. One of the example is cited here which is Import alert 53-12 is issued by US FDA which states that "Detention without Physical Examination of Black Hair Cream from the Dominican Republic[12]". FDA laboratory analyses revealed the product to contain an undeclared, unidentified, and non-certified black color[13]. Similar import alert was issued for a hair product called as hair naturalizer which had several consumer complaints such as hair loss and burning of scalp. Review of labeling for the naturalizer with color enhancer revealed the product is promoted to restore the natural black color to hair. The colorant, identified was "concentrate extract of coulteria tinctoria" in the ingredient declaration, is a vegetable dye for which no color additive regulation has been established[14]

These are specifically related to violative use of color additives in products and these are discussed in this review article to show the strictness with which finished drug products, foods & cosmetics are not only scrutinized before import to US but these are religiously practiced and thus the maintenance of quality standards with respect to color additives. Therefore, whenever such violation is found in product that hampers the quality of final product, warning letters are issued to manufacturer. Example of one such warning letter is provided below:

5.1 Example of Warning letters issued by US FDA

US FDA had assigned a warning letters to company or firm carrying out or publishing violative use of certain colour for cosmetic or for commercial purpose. For example, in one of the warning letter, it was stated by FDA administrative to BASF[15] as "Specifically, the composite pigments described on your web site are distinct color additives subject to premarket approval. Although the resultant pigments might include some chemical components similar to those listed as color additives exempt from certification in Part 73, the manufacturing processes for the composite pigments do not comply with the specifications in any current listing for cosmetics use. FDA recently listed composite pigments made from synthetic iron oxide, titanium dioxide, and mica, similar to your Cloisonne®, Cosmica® and Flamenco® products. These mica-based pearlescent pigments were listed as color additives for use in drugs (21 CFR 73.1128) and foods (21 CFR 73.350)[16]. These color additives have not been listed for cosmetic uses. Furthermore, based on the agency's experience with the manufacture of pigments, such as mica-based pearlescent pigments, whereby the coating on the substrate mica is formed *in situ* by the addition of starting compounds and the application of heat or other physio-chemical processes, the agency is aware that residues are commonly formed as a result of the manufacturing process. The safety determination for the color additives must include consideration of such residues when used as cosmetics. You should take prompt action to correct these violations. We request that you respond within 30 days from receipt of this letter with your planned corrective actions".This warning letter explains

clearly the reasons for issuance of warning letter and forces manufacturer to think rationally for appropriate use of color additive. It also shows that any such claims on website for products containing violative color additives should also be avoided[17].Further, US FDA scientists take up an analytical developmental study whenever required for these color additives. For example, they developed an analytical method, published in 2009, for measuring the amount of lead in lipstick[18] and, confirm that the amount of lead found in lipstick is very low and does not pose safety concerns. FDA limits lead in color additives to maximum specified levels, typically no more than 20 parts per million (ppm) for color additives approved for use in cosmetics.

6. SPECIFIC LABELING INSTRUCTIONS

Several coal-tar hair dye ingredients have been found to cause cancer in laboratory animals. The FDA regulation required that hair dyes containing 4-MMPD should have following label warning on the hair dye product containing this color additive[19].

"Contains an ingredient that can penetrate your skin and has been determined to cause cancer in laboratory animals".

With respect to labeling, US FDA specifies to write the warning statements and precautions for colors known to cause allergic or trigger reactions. For example, "For prescription drugs for human use containing FD&C Yellow No. 5 that are administered orally, nasally, vaginally, or rectally, or for use in the area of the eye, the labeling required by § 201.100(d) shall bear the warning statement "This product contains FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons[19]. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity." This warning statement should appear in the "Precautions" section of the labeling".

7. EUROPEAN REGULATIONS FOR COLORING AGENTS IN PHARMACEUTICALS

European parliament appointed EuropeanCommissionin order to set the regulations on food additives and established common authorization procedure for food additives, food enzymes and food flavorings (EC) No 1333/2008). As per this regulation, it was required to have specifications (as previously developed for food additives as per Commission Directive 2008/128/EC of 22 December 2008) to be laid down for specific purity criteria concerning colors for use in foodstuffs[20,21]. There were modifications to some of the colours. For example; Food colours ethyl ester of beta-apo-8'-carotenic acid (E 160 f), and brown FK (E 154), as well as the aluminium containing carrier bentonite (E 558) are not to be used any further as per information submitted by food manufacturers to European union. Thus, the specifications of the colors are given this annexure to this regulation. Few examples of specifications and their requirements as per EU regulation are listed. It describes the definition of that particular color, its brief manufacturing process in order to identify the standard starting materials for the same and specifications to which it should comply.

Example 1: Aluminium lakes for use in colours, only where explicitly stated

Definition: Aluminium lakes as given in EC states that it is prepared by reacting colours complying with the purity criteria set out in the appropriate specification monograph with alumina under aqueous conditions. Further, it also mentions the conditions for preparation of alumina. It is required as per EC regulation that the alumina should be freshly prepared undried material which is made by reacting aluminium sulphate or chloride with sodium or

calcium carbonate or bicarbonate or ammonia. Following lake formation, the final product should be filtered, washed thoroughly with water and dried. It allows for the provision of the unreacted alumina in the finished product. Besides these it mentions specifications for following residues with its limits. These are as follows:

i. **Hydrochloride (HCl) insoluble matter** : Not more than 0.5 %
ii. **Sodium hydroxide (NaOH) insoluble matter** : Not more than 0.5 %, for E 127 erythrosine only
iii. **Ether extractable matter** : Not more than 0.2 % (under neutral conditions)

Example 2: E 100 CURCUMIN

Synonyms: CI Natural Yellow 3; Turmeric Yellow; Diferoyl Methane

Definition: Curcumin is obtained by solvent extraction of turmeric i.e. the ground rhizomes of strains of *Curcuma longa* L. In order to obtain a concentrated curcumin powder, the extract is purified by crystallization. The product consists essentially of curcumins, i.e. the colouring principle (1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-dien-3,5-dione) and its two desmethoxy derivatives in varying proportions. Minor amounts of oils and resins naturally occurring in turmeric may be present. Curcumin is also used as the aluminium lake; the aluminium content is less than 30%. Only the following solvents may be used in the extraction: ethylacetate, acetone, carbon dioxide, dichloromethane, n-butanol, methanol, ethanol, hexane, propan-2-ol.Specifications listed as per EC regulation for Curcumin are provided in below table 6:

Table 6: Specifications of Curcumin as per EC recommendations

Color Index No	75300
Chemical name	I - 1,7-Bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione II 1-(4-Hydroxyphenyl)-7-(4-hydroxy-3-methoxy-phenyl-)hepta-1,6- diene-3,5-dione III 1,7-Bis(4-hydroxyphenyl)hepta-1,6-diene-3,5-dione.
Chemical formula	I C 21 H 20 O 6 II C 20 H 18 O 5 III C 19 H 16 O 4
Molecular weight	I. 368,39 II. 338,39 III. 308,39
Assay	Content not less than 90 % total colouring matters E *1% 1cm* 1 607 at ca. 426 nm in ethanol
Description	Orange-yellow crystalline powder
Identification	Maximum in ethanol at ca. 426 nm
Purity	
Solvent residues	Ethylacetate Not more than 50 mg/kg, singly or in combination Acetone n-butanol

	Methanol Ethanol Hexane Propan-2-ol 9 Dichloromethane: not more than 10 mg/kg
Arsenic	Not more than 3 mg/kg
Lead	Not more than 10 mg/kg
Mercury	Not more than 1 mg/kg
Cadmium	Not more than 1 mg/kg

Note: Aluminium lakes of curcumin color may be used.

As per EU regulation, there are "E" numbers which are identified along with their names. Below table 7provides the list of few of the colors with their E numbers.

Table 7: Common name of color with assigned E number as per EU regulation:

E numbers	Name of the color
E100	Curcumin
E101	(i) Riboflavin
	(ii) Riboflavin-5'-phosphate
E102	Tartrazine
E104	Quinoline yellow
E110	Sunset Yellow FCF; Orange Yellow S
E123	Amaranth
E124	Ponceau 4R; Cochineal Red A
E127	Erythrosine
E129	Allura Red AC
E131	Patent Blue V
E132	lndigotine; Indigo Carmine
E133	Brilliant Blue FCF
E151	Brilliant Black BN; Black PN
E154	Brown FK
E155	Brown HT
E160a	Carotenes
E160b	Annatto; Bixin; Norbixin
E163	Anthocyanins
E170	Calcium carbonate
E171	Titanium dioxide
E172	Iron oxides and hydroxides
E173	Aluminium
E174	Silver
E175	Gold
E180	Litholrubine BK

Further as per EU guideline, Medicinal products for human use, safety and environment, volume 3 B, july 2003, colouring agents are considered as excipients along with other constituents of dosage form such as preservatives, stabilizers etc. As per this guideline there are labeling requirements to be followed for coloringagents[22]. Following is the labeling requirement for azo dyes colors (Refer Table 8) as per guidelines. With respect to colorants for cosmetics, European union have formed the regulation on cosmetic products. In this regulation, there are specific requirements for colorants in cosmetics which states that "To avoid ambiguities, it should be clarified that the list of allowed colorants contained in Annex IV includes only substances which color through absorption and reflection and not substances which color through photoluminescence, interference, or chemical reaction" and " To avoid ambiguities, it should be clarified that the list of allowed colorants contained in Annex IV includes only substances which color through absorption and reflection and not substances which color through photoluminescence, interference, or chemical reaction[23]".

Table 8: Labeling requirements for Azo dyes as per EU regulation[22]

Name	**Route of administration**	**Threshold**	**Information for package leaflet**
Azo colouring agents (eg: E102, tartrazine E110, susnset yellow FCF E122, azorubine, carmoisine E123, amaranth E124, ponceau 4R red, cochineal red A E151 brilliant black BN, black PN	Oral	Zero	May cause allergic reactions

8. INDIAN REGULATION FOR USE OF COLORING AGENTS IN DRUGS & COSMETICS:

As per regulatory requirement by government of India for use of coloring agents in pharmaceuticals, it forms the part of Drugs & Cosmetic act 1940, rules 1945, amended as on 30th June 2005. As per this act, coloring agents allowed for usage in drugs and cosmetics are classified into four types[24]:

1. Natural colours
2. Artificial colours
3. Coal-tar colours
4. Lakes.

These all colors are listed under "Rules 127" of D&C act 1940. Out of these four types, only for coal tar colors, additional details such as chemical name, color index number and common name is provided.

Rule 127 clause (2) of the Drugs and Cosmetics Rules 1945 mentions that the label on the

container of a *drug* containing a permitted colour shall indicate the common name of the colour, for example: Quinazarine Green SS, Tartrazine, Erythrosine etc. But, the same is not true with cosmetics. No direction is given in the D&C Act and Rules regarding the nomenclature of a colouring agent. *Pond's White Beauty cream* (Hindustan Unilever Ltd.) mentions CI 14700 on the label. *Garnier Wrinkle Lift anti-ageing cream* (Loreal India Pvt. Ltd.) does not mention any colour. *Lactocalamine* (Nicholas Piramal India Ltd.) mentions the colour on the label as "permitted colour". *New Ever Youth Orange Peel Off Skin Vitalizer* (Cadila Healthcare Ltd.) does not mention any colour. These examples prove that there is no harmonization in the nomenclature of colourants in India[26].
Below table 9covers list of few of the colors listed as per current regulatory requirement for drug products marketed in india [27].

Table 9: List of colors approved as per D&C act 1940.

Listed Natural colors	**Listed Artificial colors**	**Listed Coal-tar colors**			**Lakes**
		Common name	**Chemical name**	**Color index number**	
Annatto	Caramel	**GREEN** Quinazarine Green S.S.	1, 4-bis (p-Toluino) anthraquinone.	61565	Aluminium or calcium salts of any water soluble listed colours. Labeling requirement for lakes is that it's common name should be included
Red Oxide of iron		Alizarin Cyanine Green F.	Disodium salt of 1, 4-bis (O-sulfo-p-Toluino) anthra-quinone.	61570	
Yellow Oxide of iron		Fast Green F.C.F.	Disodium salt of 4-{[4-(N-ethyl-p Sulfobenzylamino)-phenyl-]-(4-hydroxy-2- sulfoniumphenyl)-methylene} [1-(N-ethyl-N-p-sulfobenzyl]Δ 2,5-cyclohexadienimine].	42053	
Titanium Oxide		**YELLOW** Tartrazine	Trisodium salt of 3-carboxy-5- hydroxy-l-p-sulfophenyl-4-p-Sulfophenyl azopyrazole.	19140	
Black Oxide of iron	Riboflavin	Sunset Yellow FCF	Disodium salt of 1-p-sulfophenyl azo-2-naphthol-6-sulfonic acid.	15985	--

Further, as per schedule Q of drugs & cosmetics act 1940, following are the list of colours approved for use in cosmetics and soaps and this is as per *IS : 4707 (Part I)-1988 as amended by the Bureau of Indian Standards.* Refer table 10and 11for colors approved for cosmetics and soaps respectively as per schedule Q[27] .

Table 10: Approved colors for cosmetics formulations as per schedule Q.

Common name	Colour index number	Chemical name.
Guinea Green B	42085	Monosodium salt of 4-(N-ethyl-p-sulfobenzylamino)–diphenylmethylone-(1-(N-ethyl-N-p-sulfoniumbenzyl)Δ 2,5-cyclohexadienimine).
Light Green SF Yellowish	42095	Disodium salt of 4-[4-(N-ethyl-p-sulfobenzylamine)-phenyl)-4-sulphoniumphenyl) methylene]-2(-(N-ethyl-N-sulfobenzyl) Δ 2,5-Cyclohexadienimine.
Tartrazine	19140	Trisodium salt of 3-carboxy-5-hydroxy-1-p-sulfophenyl-4-p-sulfophenylazo-pyrazole.
Sunset yellow FCF	15985	Disodium salt of 1-p-sulfophenylazo-2-naphthol-6-sulfonic acid.
Ponceau 3R	16155	Disodium salts of a mixture of 1-alkyl-phenylazo-2-napthol 3, 6-disulfonic acids.
Lake Red D.	15500	Monosodium salt of 1-0-carboxyphenylazo-2-naphthol.
Lake Red DBA	15500	Barium salt of 1-o-carboxyphenylazo-2-naphthol.
Lake Red DCA.	15500	Calcium salt of 1-o-carboxyphenylazo-2-naphthol.

Table 11: Approved colors for soaps as per schedule Q.

Common name	Colour index number	Chemical name.
Phthalocyanine Blue	74160	(phthalocyninate (2--) copper.
Iragalite Red CVPB Paste or Pigment Orange 5	12075	1-(2,4-dinithro phenylazo)-2-Naphthalenol.
Citrus Red No.2.	12156	1-2(2,5-dimethoxy phenylazo) 2-naphthol.
Rhodamine B 500	45170	3-ethochloride of 9-0 carboxy-ethenyl-6-diethylamino-3-ethylamine-3-isoxanthene.
Aqueous Green Paste	74260	Polychloro copper Phthalocyanine.
Pigment Yellow 3	11710	2-(4-Chloro-2-nitrophenyl)-azo-N-(-2-Chloro-phenyl)-3-Oxobutamide.

9. CONCLUSION

Coloring agents have evolved from concept of its use to hide or mask unwanted color to its modern day technical use as protective agent, correct dosage form identification etc. it is necessary to understand the chemistry behind each color, its correct nomenclature and its applications. This would be useful to industry researchers to select correct grade of color from its pre-formulation stage itself. Further, as now it is very common to manufacture drug product in one territory and market it in other parts of world, therefore, this understanding of color nomenclature and use in prescribed geographic locations would provide better applications of these agents and finally better regulatory and overall patient compliance with respect to safety standards. Thus it is very important to understand the upcoming significance required for judicious and precise use of coloring agents for pharmaceutical dosage forms for worldwide pharmaceutical market.

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