Medical Device Color Additives
SOT-MDCPSS -Webinar

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Manual

Plan on teaching a color additive course?

Please appropriately acknowledge/reference this Webinar and supporting publications

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Interstate Commerce

- Section 201(b) of FFDCA (21 USC 321(b))
- "(1) commerce between any State or Territory and any place outside thereof, and
  (2) commerce within the District of Columbia or within any other Territory not organized with a legislative body."
- "Interstate commerce" applies to all steps in a product's manufacture, packaging, and distribution

Adulteration

How does the law define this for color additives?

Adulterated:

- Unsafe per Section 721(a) of FFDCA (21 USC §379e); not otherwise compliant with the FFDCA or FDA's regs (e.g., A product can be considered "adulterated" because it contains a color additive that is not batch certified by FDA (FFDCA Sec 303)
- Other reasons device can be considered adulterated
  - FFDCA Sec. 501 (21 USC Sec 351)

Unsafe

- Color additives are considered “adulterated” if they are “unsafe” [per 21 USC 379e(a), FFDCA Section 721(a)]
- Per Delaney Clause (carcinogens) [21 USC 379e(b)(5)(B)]
- Defined in terms of “safe” [21 CFR §70.3(i)] – “convincing evidence that establishes with *reasonable certainty that no harm* will result from the intended use of the color additive.”

Misbranding

- **See FFDCA Sec 502 (21 USC §352, especially 21 USC §352 (m))**
- **Misbranding**: A drug or device shall be deemed to be misbranded (a) if its labeling is false or misleading in any particular; (b) if in package form unless it bears a label containing (1) the name and place of business of the manufacturer, packer, or distributor; and (2) an accurate statement of the quantity of the contents in terms of weight, measure, or numerical count; (c) If any word, statement, or other information required by or under authority of the Act to appear on the label is not prominently placed thereon with such conspicuousness and in such terms as to render it likely to be read and understood by the ordinary individual under customary conditions of purchase and use...

(http://www.fda.gov/forconsumers/consumerupdates/ucm268130.htm)

21 USC §379e

- http://www.gpo.gov/fdsys/pkg/USCODE-2010-title21/pdf/USCODE-2010-title21-chap9-subchapVII-partB-sec379e.pdf

Critical Legislative/Regulatory Milestones in Medical Device History

1906	**Pure Food and Drugs Act** enacted	Mostly simple tools on the market (stethoscope, scalpels, etc.) Devices not included in Act
1938		
1960	**Federal Food, Drug & Cosmetic Act** (FFDCA) enacted	Defines "medical device" Forbids sale of therapeutic devices that are dangerous or marketed with false claims ("adulterated"/"misbranded").
	Manufacturers responsible for determining if products are safe and effective. "Radium belt" – claimed to prevent appendicitis, gallbladder disease or anything that might ail its wearer. Enforcement action to get such devices off market was restricted to FTC & Post Office. FDA, itself, could do nothing.	
1962	**FFDCA Color Additive Amendments**	
1969	President Kennedy proposes changes to FFDCA so that they could be regulated separately, but comparably, to drugs. However, drug issue needs related to thalidomide eclipsed those of devices. **Drug Amendments (Kefauver Harris)** enacted – premarket approval for safety and effectiveness.	
1972-1975	President Nixon & "Cooper Committee" → Congress… FDA, itself, starts classifying devices according to risk and gets Congress' attention	
	Pacemaker failures. Dakon Shield IUD injuries	
1976	**Medical Device Amendments** become Law	
1978	**Good Manufacturing Practice regulations** published in Federal Register (based on 1976 Medical Device Amendments)	
1997	**Quality System Regulation** (QSR) takes effect	

Delaney Clause
21 USC § 379e(b)(5)(B)

A color additive (i) shall be deemed unsafe, and shall not be listed, for any use which will or may result in ingestion of all or part of such additive, if the additive is found by the Secretary to induce cancer when ingested by man or animal, or if it is found by the Secretary, after tests which are appropriate for the evaluation of the safety of additives for use in food, to induce cancer in man or animal, and (ii) shall be deemed unsafe, and shall not be listed, for any use which will not result in ingestion of any part of such additive, if, after tests which are appropriate for the evaluation of the safety of additives for such use, or after other relevant exposure of man or animal to such additive, it is found by the Secretary to induce cancer in man or animal.[41]

21 USC §379e(b)(5)(A)

- Congress noted relevant factors FDA needs to consider in determining safety of a color additive for its proposed use, e.g.,
  - Exposure information
  - Safety factors (expert opinion)
  - Appropriate analytical methods for determinations of identity and quantity of pure dye (and its intermediates and impurities contained in the color additive)

Legislative Color Additive Milestones

Pure Food & Drug Act Voluntary batch certification of synthetic color additives used in food.	1906
Federal Food, Drug & Cosmetic Act (FFDCA) Mandatory batch certification of color additives used in food, drugs and cosmetics.	1938
FFDCA Color Additive Amendments Introduced requirement for food, drug and cosmetic manufacturers (NOT device manufacturers) to submit to procedures to ensure the safety of color additives used in their products. Premarket approval of all color additives; introduction of exemptions from color additive batch certification; color additives in use at this time placed on "provisional" list, pending demonstration of their safety or lack of safety.	1960
FFDCA Drug Efficacy Amendment ("Kefauver Harris Amendment") Introduced requirement for drug manufacturers to demonstrate the effectiveness and safety of their drugs before approval; set precedent for device preapproval processes.	1962
FFDCA Medical Device Amendments Medical devices integrated into FFDCA; requirement for premarket approval and compliance with color additive regulations for devices with body contact of "significant duration"	1976

FFDCA definition of “Medical Device”

“… instruments, apparatus, and contrivances, including their components, parts and accessories, intended (1) for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or animals; or to affect the structure of any function of the body of man or other animals.” *FFDCA, 1938*, P.L. 75-717.

Substantial Equivalence per FDA regs

(21 CFR Part 807 Subpart E)

A device is substantially equivalent if, in comparison to a predicate it:

- has the same intended use as the predicate; **and**
- has the same technological characteristics as the predicate; **or**
- has the same intended use as the predicate; **and**
- has different technological characteristics and the information submitted to FDA;
  - does not raise new questions of safety and effectiveness; **and**
  - demonstrates that the device is at least as safe and effective as the legally marketed device.

1976 Medical Device Amendments to FFDCA: Color Additives Language

Sec. 9 (a) Section 706 is amended (1) by inserting "or device" after "drug" each time it occurs, (2) by inserting "or devices" after "drugs" each time it occurs, and (3) by adding at the end of subsection (a) the following new sentences: "*A color additive for use in or on a device shall be subject to this section only if the color additive comes in direct contact with the body of man or other animals for a significant period of time* [emphasis added]. The Secretary may by regulation designate the uses of color additives in or on devices which are subject to this Section." (b)(1) Section 501(a) is amended (A) by inserting "(3) if its" in lieu of "(3) if it is a drug and its"; (2) by inserting "(4) if (A) it bears or contains" in lieu of "(4) if (A) it is a drug which bears of contains"; and (3) by inserting "or devices" after "drugs" in subclause (B) of Clause (4). (2) Section 502 (m) is amended by striking out "in or on drugs."

“Color Additive” vs. “Colorant”

- A personal pet peeve
- “Color additive” does not have the same legal or regulatory definition as “Colorant”
- FDA’s regs use the term “colorant” to colors added to food contacting polymers (*See 21 C.F.R. § 178.3297(a) (2014) (describing “colorants for polymers”); see also 21 C.F.R. § 314.420 (Drug Master File “excipient”)*

21 CFR §70.3(f)
Defn almost ID to 721(a) FFDCA

A *color additive* is any material, not exempted under section 201(t) of the act, that is a dye, pigment, or other substance made by a process of synthesis or similar artifice, or extracted, isolated, or otherwise derived, with or without intermediate or final change of identity, from a vegetable, animal, mineral, or other source and that, when added or applied to a food, drug, or cosmetic or to the human body or any part thereof, is capable (alone or through reaction with another substance) of imparting a color thereto.[60]

21 USC § 321(t)
language was not changed in 1976

Section 201(t) of the FFDCA, as amended (21 U.S.C. § 321(t)) defines "color additive"[54] as follows

(1) The term "color additive" means a material which—

(A) is a dye, pigment, or other substance made by a process of synthesis or similar artifice, or extracted, isolated, or otherwise derived, with or without intermediate or final change of identity, from a vegetable, animal, mineral, or other source, and

(B) when added or applied to a food, drug, or cosmetic, or to the human body or any part thereof, is capable (alone or through reaction with other substance) of imparting color thereto; except that such term does not include any material which the Secretary [of the Department of Health and Human Services], by regulation, determines is used (or intended to be used) solely for a purpose or purposes other than coloring.[55]