Medical device color additives: Legal and regulatory aspects

Brenda Seidman, M.S., Ph.D., RAC

Seidman Regulatory Toxicology

bcseidman@gmail.com 202.699.1051

Introduction

- Today's presentation is result of self-assigned research/writing project
- My interest is in regulatory toxicology
- Regulatory science is not always rational or free of politics

Introduction

- Why would I take on this research project?!
  - Always confused about CDRH's color additives practices
  - No primary literature
  - Complimented studying for RAC
  - CDRH's recent practices & draft guidance on the use of ISO-10993 (Section 7) in April 2013

Two recent papers – Food Drug Law Institute (FDLI)

"The Grays of Medical Device Color Additives" B. Seidman (Nov 2014). Food and Drug Law Journal

"Medical Device Color Additives: What's All the Ruckus About?" B. Seidman (Jan 2015). Food and Drug Policy Forum

Objectives of research

1. Review legal and regulatory framework for medical device color additives

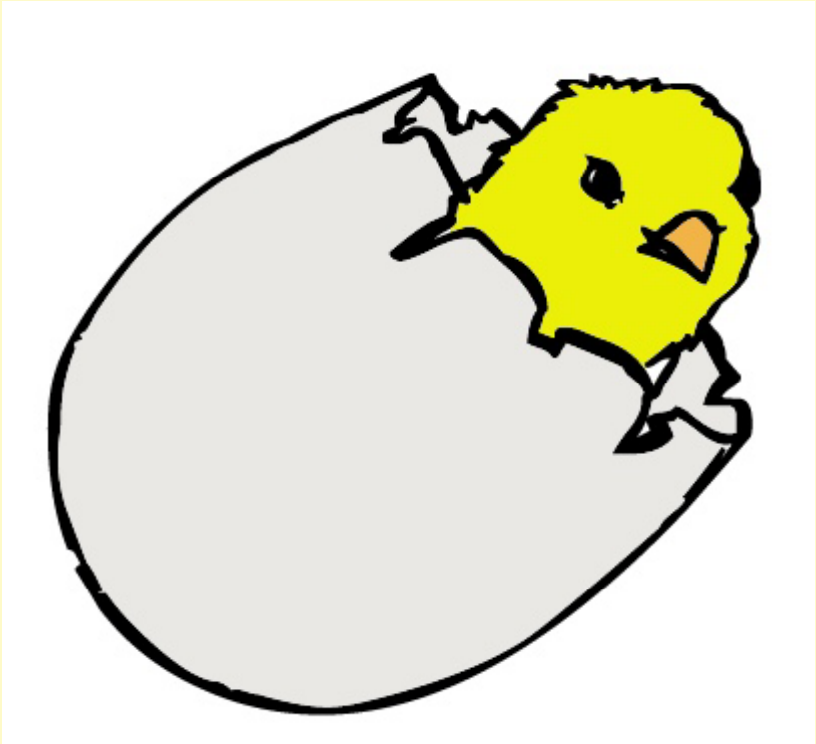
2. Identify medical device color additive practices within FDA, both historically and currently

Objectives of research

3. Understand CDRH's Section 7 of April 2013 draft guidance - Use of ISO 10993

4. Consider if current practices
   - consistent with law and FDA regulations
   - make sense

CDRH's April 2013 Draft Guidance & recent practices did not just "hatch"



CDRH's past drives its current approaches

Laws

Regs

Litigation

Political appointees

Policies/practices

Today's Topics

Big picture stuff

- Color uses in medical devices
- Laws, regulations, policies, practices

Today's Topics

The minutiae

- History of color additive laws
- Wiley Act
- FFDCA & amendments
- Significant color additive case law
- Medical Device Amendments of 1976
- The Delaney Clause
- FDA Regulations
- CDRH & CFSAN historical color additive practices
- Understanding color additives' section of CDRH's 2013 "Use of…" draft guidance

Today's Topics

Suggestions and discussion

- How to deal with colors in devices already on market?
- Dealing with color in devices prospectively

Color Additives - Uses

- Medical Devices
- Food
- Drugs
- Cosmetics

Color Additives – Uses in Medical Devices

- Human factors
  - Visual coding (e.g., connecting pieces of a devices; drug delivery devices)
  - Locating device *in situ*
  - Markers
- Cosmetic (contact lenses)
- Consumer preference/perceived consumer preference
- Branding
- Subtle marketing/reinforcement of marketing

Historical sources of food, drug, cosmetic colors

Vegetable and mineral

Paprika, turmeric, saffron, iron oxides, lead, antimony-containing compounds, copper ore, vegetable extracts

Metal salts

Lead, arsenic, copper, mercury

Synthetic colors

Coal tar derivatives originally… think *polycyclic aromatic hydrocarbons*

Legal interest in colors: Foods

Began with food – consumer fraud & then safety

- England, era of King Edward I (1272-1307)

  "If any default shall be found in the bread of a baker in the city, the first time, let him be drawn… through the streets… with the faulty loaf hanging from his neck…."

Legal interest in colors: Foods

- France (1396 & 1574)
  - Laws forbade coloring
    - of butter (1396)
    - In pastries to suggest presence of eggs (1574)
- England – Chemist-activist, Friedrich Accum (1820)
  - Treatise of Adulterations of Food and Culinary Poisons
  - Concerned with poisonous dyes & fraud (e.g., lead, copper & arsenic coloring of kids' candies)

Legal interest in colors: Foods

- England, Physician-activists, Thomas Wakley and Arthur Hill Hassall (mid-1800s)
  - Concerned with “perpetual fraud” and use of brightly colored poisonous candies targeted to children
- England, Parliament (1860). 1st modern law
  - Acknowledges problem, but no enforcement

Legal interest in colors: Foods

- England, Parliament
  - Sale of Food and Drugs Act (1875) – criminal sanctions
  - Food Adulteration Act (1899) – active oversight, penalties
- U.S. (1881)
  - Government begins investigating, but toxic colored metal salts were in common use until 1906.
- **U.S. (1906) – Wiley Act (aka Pure Food and Drugs Act)**
- **U.S. (1938) – Federal Food, Drug and Cosmetic Act (FFDCA)**
- **U.S. (1960) – Color Additive Amendments**

U.S. Legislation that Addresses Color Additives

- Was never food-specific, but emphasis has always been on food
- 1976 – Medical Device Amendments
  - Devices brought into FFDCA "fold"
  - Includes color additive provisions, as well as Delaney Clause

What drives FDA practices?

- Legislation
- Regulations & guidance documents
- Litigation
- Agency culture and its policies
- Political appointees

Laws, regulations, policies, practices

Congress

- Bills
- *Writes, +/- Passes Act*

President

Signs/vetoes

↓

Law/Statute

(recorded in U.S. Code)

FDA

Implementation & Enforcement

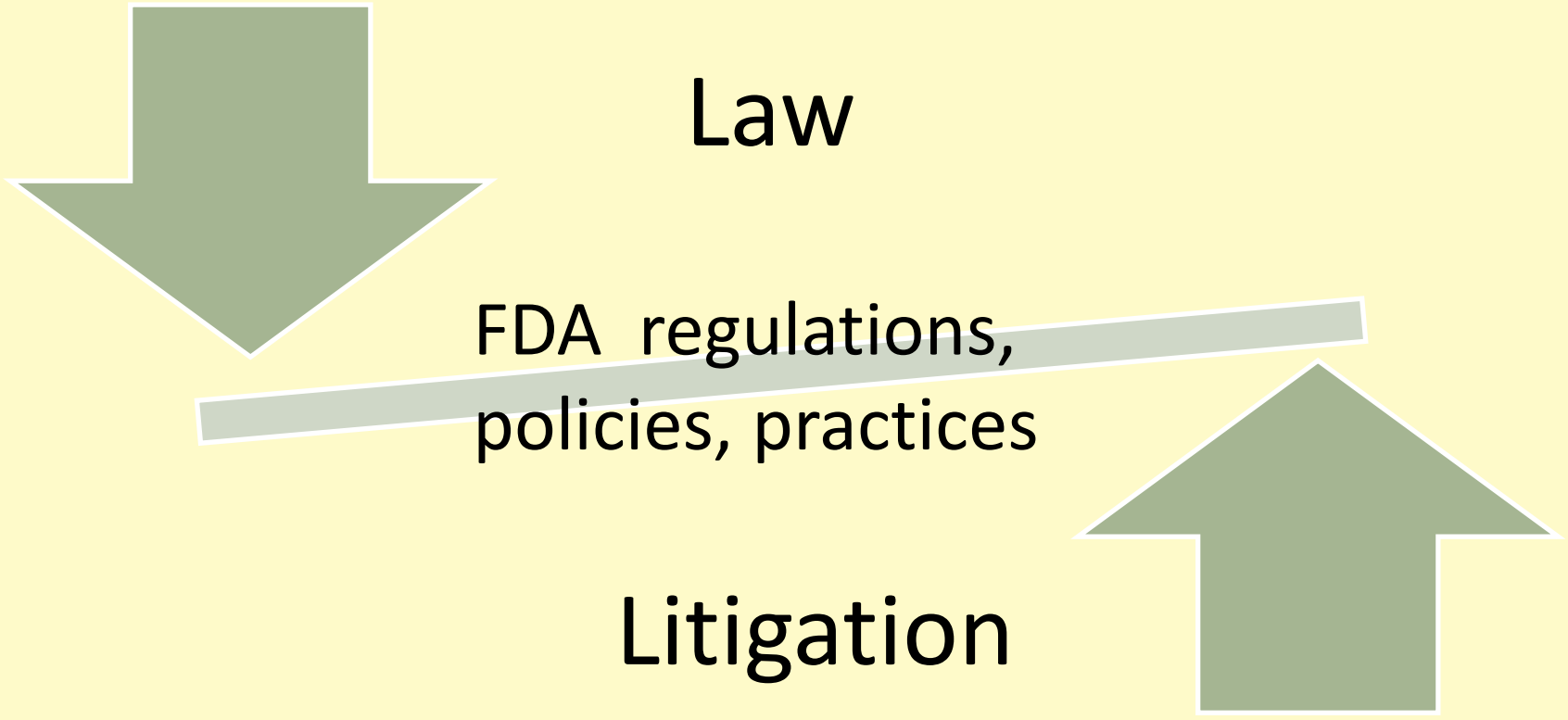
Rulemaking; Regulations (Federal Register → Code of Federal Regulations, Title 21 - e.g., 21 C.F.R. Part 73)

- Policies (e.g., guidances)
- Practices
  - *"enforcement discretion"*

Nothing stays the same

- Laws change
  - Lobbying
  - Litigation
- Political appointees change
- Regulations change
- Agency policies and practices change

Influence of Litigation on FDA Implementation of Statute



Color additives on the books decades before applicable to devices

- 1881
  - USDA begins investigating color additives (mostly toxic metal salt colors)
- **Wiley Act (1906). "Pure Food and Drugs Act"**

The Wiley Act, 1906

- First US legislation to deal with colors
- Addresses colors in foods *and* drugs (not devices)
  - Outlaws use of toxic metal salt colors
  - Voluntary batch certification of synthetic colors
  - Criminal penalties for **interstate commerce** of foods & drugs that are:
    - **adulterated**
    - **misbranded**
    - "poisonous"
    - "deleterious"

Interstate Commerce, Adulteration, Misbranding

Please see Manual.

Out with the old, in with the new: Early 1900s - Synthetic color additives

Shortly after Wiley passed –

- Colors derived from coal tar ("coal tar" colors)
  - Fill toxic metal salt color additives void
  - Easier to manufacture
  - Less expensive to make

Coal tar colors:
USDA (FDA)

- Had been used primarily in textile industry
- Not much was known about their safety
  - USDA's Bureau of Chemistry's* important work - 1907
  - Of 80 then used in food, only 7 could be considered acceptable for that use
  - USDA proposes a testing and certification process

*FDA originated from this Bureau

Coal tar colors:
Toxicologists & epidemiologists

- Animal studies on individual chemicals (polycyclic aromatic hydrocarbons) from coal tar mixtures demonstrate they're carcinogenic
  - Dibenz(*a,h)*anthracene
  - Benzo(a)pyrene
  - 2-naphthylamine
  - Aminoazotolune
  - Aminoazobenzene
- Aniline dye exposure in humans
  - Bladder cancer

FFDCA, 1938

- Defined “devices” & prohibited interstate commerce of adulterated and misbranded devices
  - Primary goal – to prevent “gadgetry quackery”
- No premarket approval of color additives
- Charged FDA with developing regulations for the listing of coal tar colors that are “harmless and suitable for use in foods.”

Example of quack device

- Orgone Energy Accumulator – size of a telephone booth; patient sat inside
  - Claimed device could gather energy from atmosphere and cure patient of common cold, cancer, impotence.
  - Oh well…. It's *b..a..c..k!* Now being sold online…

http://www.orgonics.com/orders.htm

FD&C Red Number 32: Role in Color Additive Amendments, 1960

- *Flemming v. Florida Citrus Exchange*, 358 U.S. 153, 157 (1958). Supreme Court.
  - Red Number 32 was a coal tar-derived color additive.
  - For coloring oranges.
  - As a result of new animal testing, FDA decided it did not consider it "harmless"
  - FDA did not consider dose-response (Agency wasn't obligated to consider a safe tolerance)
  - This caused the use to be unlawful.
  - →Lobbying to change law

Color Additive Amendments, 1960

- Premarket approval of all color additives
  - For food, drugs, cosmetics (not devices at this point)
- Mandated procedures very similar to USDA's recommendations in early 1900s
  - Listing of color additives (with specifications)
  - Certification
  - Petition procedure
- Includes Delaney Clause for carcinogens
  - from Food Additives Amendment of 1958

FFDCA's Definition of "Color Additive" (21 USC §321 (t))

(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]

Delaney Clause

- 1958 – Delaney Clause added to the FFDCA as part of the Food Additives Amendment
- 1960 – Incorporated into the FFDCA as part of the Color Additive Amendments [21 USC 379e(b)(5)(B)]
  - Food, drugs, cosmetics
- 1976 – Applies also to devices (Medical Device Amendments; 21 USC 379e(b)(5)(B))

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]

Delaney Clause
21 USC 379e(b)(5)(B)

- "A color additive (i) shall be deemed unsafe ... if the additive is found ... to induce cancer...."
  - in human or animal

- Science vs the Law
  - The presence of a color additive is a function of analytical chemistry
  - Carcinogens in animals are not always carcinogens in humans
  - Some chemicals can cause cancer at one dose, but not at a lower dose

Major color additive Delaney litigation

- *Scott v FDA,* 1984
- *Public Citizen v Young,* 1987

If a color additive, *itself*, is carcinogenic, Court unwilling to allow FDA administrative discretion (*de minimis*, risk assessment)

Medical Device Amendments, 1976

Amended FFDCA to address devices

- An attempt to ensure device safety and effectiveness through HHS (FDA) regulation
- Device classification & classification panels
- Performance standards
- Premarket submissions & approvals
  - IDEs, PMAs, 510(k)s
- Devices are spliced into FFDCA's color additive's language with a twist

Medical Device Amendments 1976 FFDCA 21 U.S.C. § 379e(a)(2)

Did Congress intend all devices that used color additives to be regulated?

"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."

“Direct contact”

- Local contact (device-skin; device-blood, etc.)
- Other contact (leaching, ISO’s “indirect” contact)
  - Free color additive
    - Consideration of effective dose?
    - Analytical abilities to detect chemicals have dramatically improved since 1976
      - Becomes an issue with the Delaney Clause

“Significant period of time”

- FDA has not defined in a regulation, guidance, draft guidance
  - >30 days?

- ≥ 30 days
  - ISO 10993-1, “permanent” category?

Overview of FDA Color Additive Regulations

- Certification
- Petitioning
- Listing

Color Additive Regulations

The regulations: 21 CFR Parts 70, 72-74, 80-82

- CERTIFICATION. 21 CFR Part 80
  - Applies to devices, food, drugs, cosmetics
- PETITION. 21 CFR Part 71
  - Applies to devices, food, drugs, cosmetics
- LISTING for devices.
  - 21 CFR Part 73, Subparts B&D (*exempt* from certification)
  - 21 CFR Part 74, Subpart D (*subject* to certification)

Certification
21 CFR Part 80

- FDA may need to verify that the batch of color additive a manufacturer plans to use conforms to the color additive listing: "certification" process (FDA does the chemical analysis)
  - "not exempt" 21 CFR Part 74
- Certification *not* required for color additives
  - "exempt" 21 CFR Part 73

Petition & Listing
21 CFR Part 71
21 CFR Parts 73 & 74

- If a color additive is not listed in the CFR for a specific use, one is expected to petition CFSAN in order to get it listed
- Usually, it is the color additive manufacturer who petitions
- Process separate from the device premarket clearance or approval

Petition & Listing
21 CFR Part 71
21 CFR Parts 73 & 74

- Outcome of a successful petition is the listing of that color in the CFR
  - Specific use
  - Specific conditions of use
- Generally recognized as safe (GRAS) is not applicable

Is the color in your device a listed color additive?

- Unlikely
- The only devices for which colors additives are listed in the CFR:
  - Contact lenses
  - Surgical sutures
  - Intraocular lens haptics
  - Bone cement
  - Absorbable meniscal tacks

Is the color in your device a listed color additive?

- 25 color additives listed & exempt from cert.
- 9 color additives listed & not exempt
- Approved for use on $\geq$ 1 of 5 types of medical devices

Making sense of an apparent lack of compliance

Possibilities

Device manufacturers:

- Submit unsuccessful petitions
  - use the color anyway
  - don't use the color
- Use color additives that are approved for their specific device types
- Use already listed color additives for uses in specific devices for *other* device types
- *Use color additives listed for foods, drugs, cosmetics in devices*
- *Use colors that are not listed at all*

Regulations for 510(k)s, PMAs and IDEs

- *Each different for color additives (appearances are deceiving – depends what one is referring to)*

Historical Expectations: PMA, IDE, 510(k)

- PMA device. 21 C.F.R. § 814.20(f)). Listed color additive a requirement
- IDE device. 21 C.F.R. §812.1. FDA enforcement discretion
  - see Manual – Walter Snesko document, 1995: "consistent with needs of public health.")
- 510(k) device. 21 C.F.R. § 807.87. Nothing in the regs., but there was policy and there have been practices
  - Have they historically been applied uniformly?
  - Do they make scientific sense?

Historical Expectations: 510(k)s

OK, as long as the color "is listed" (perhaps with some testing or other assessments)

– Practice still in place? Rules known to all?

Was/is the science solid?

- Does it make sense that a color additive approved for food use is toxicologically equivalent to that same color additive when used in a cardiovascular stent?
- Does route difference play a role?
  - Role of first-pass metabolism?
  - Absorption differences?

Historical Practices: PMAs & IDEs

- Even for PMAs and IDEs, some reviewing divisions and reviewers may have treated color additives as if they were to be used in 510(k) devices
  - Perhaps with some additional evaluations, including testing

Origins of Medical Device Color Additives Policy

Early 1980s, FDA was working feverishly to implement the Medical Device Amendments

- Color additives - low priority
- Color additives policy developed for 510(k)s, PMAs, IDEs – regs reflect this policy.
- Most stringent for PMAs (justification: more thorough review)
- Policy was communicated to industry trade associations
- CDRH followed the policy unevenly
  - Some reviewing divisions did their own thing
  - No internal mechanism for documenting use of color additives in devices
- Manufacturers did not always identify color additives they were using

Current Shared CDRH/CFSAN Color Additive Practices

- No single FDA entity/component "owns" color additive process for medical devices
- Responsibilities split between CDRH & CFSAN
  - No memorandum-of-understanding that clearly calls out the responsibilities of each
  - CFSAN considers CDRH and medical device manufacturer, itself, to be responsible for determining if color additive petition is necessary
  - CFSAN indicates it doesn't see many device color additive petitions
    - Exceptions: contact lenses, sutures, bone cement

Manufacturers of contact lenses, sutures – Higher degree of compliance?

- Role of guidances (i.e., contact lens guidances)
- Specific language in color additive regulations for colors that come into contact with area of eye, and for surgical sutures?
  - 21 C.F.R. § 70.3(s) and § 70.5(a)
  - 21 C.F.R. § 70.5(c)
- Historical role of some of these being considered as "drugs" before 1976?
  - CDER's role?
    - Scientific culture differences

CDRH color additive practices

- Ad hoc practice still?
  - Check sheets to submitters
  - Written procedures?
    - Internal and geared to industry?
- Separate premarket approvals/notifications for device and premarket approval for color is not ideal
  - Color additive has its own preapproval process – may be longer than for device approval/clearance
  - Timing in product development is off
    - Submission/notification happens late in the game
    - Color additive selection happens early
    - Mismatch in timing can cause a major “rewind” in efforts

CDRH's Recent Interest in Color Additives

- Increased awareness that legally marketed devices use non-listed colors
- Requests of manufacturers
  - Provide specific color additive info (CAS #, CFR refs)
  - "bioavailability" information
  - For both 510(k)s and PMAs
  - For devices that have already been cleared or approved
    - Suggests CDRH cannot track historical uses of color additives in devices
- Draft Guidance. April 2013. "Use of ISO 10993" – Section 7

Section 7 – "Use of…" draft guidance

"Assessment of Known or Potentially Toxic Chemical Entities"

- Unclear & wasn't ready for "prime time"

Section 7 – "Use of…" draft guidance

- Poorly vetted within Agency?
- Does not effectively relate recommendations to regs overall
  - IDE vs PMA vs 510(k)
- Use of the word "colorant"
  - If CDRH wants to change regs to apply to "colorants" in devices, it would have needed to articulate that and explain how food packaging colorants regs can be used for device color additives

Section 7 – “Use of…” draft guidance

- Gives impression of poor understanding of Agency’s color additive regs
- Mentions CFSAN and petitions process for color additives that are “bioavailable” for more than 30 days
- Seems to *want* to treat color additives as ISO 10993 treats any other chemical

Section 7 – "Use of…" draft guidance

Does not tell us what Congress prompted FDA to tell us in 1976

- What is a "significant period of time"?
- "over 30 days" (line 925)?

Unclear use of well-established pharmacology terms

- "bioavailable," "bioavailability"
  - In blood?
  - Somewhere in body other than in device?
  - Leachates? Extractables?
  - "pharmacokinetic analyses"

Section 7 – "Use of…" draft guidance

Lines 936-939: "If the chemical is confirmed to be bioavailable, assessment(s) of the fate of the chemical in a clinically relevant animal model should be provided to assess the timing of elimination, and pharmacokinetic analyses (e.g., absorption, distribution, metabolism, and excretion (ADME))."

- Chasing around color additive molecules with little or no rationale?
- If something is not toxic, what purpose is there to evaluating pharmacokinetics for a chemical in a device?

Section 7 – "Use of…" draft guidance

CDRH (lines 948-950):

"The sponsor should identify all regulations for the particular color additive, even if the listing(s) is for a different application (e.g., different device application, use in food packaging)"

- "colorants" are in food packaging; "color additives" are in food…
- 21 C.F.R. § 178.3297(a)? Why not develop the applicability here?
- 510(k)s? IDEs? PMAs?

Section 7 – “Use of…” draft guidance

Unfortunately, input from AAMI could have been

– apparent AAMI draft standard review approach

We now have to wait to see what the final guidance looks like.

Suggestions for dealing with device color additives in future

- FDA administrative action to relieve FDA color additive responsibilities for medical devices (certification, petitioning, listing, Delaney?)
- Advocating for legislative changes
- FDA should promote use of current GMPs (Quality System Regulations 21 C.F.R. § 820) for evaluation of color additives (and other device chemicals)
  - Emphasis on evaluation of color additives should be <u>early</u> in device design & development process, e.g.:
    - 21 C.F.R. § 820.30, Design controls
    - 21 C.F.R. § 820.50, Purchasing controls;
    - 21 C.F.R. § 820.70, Production and process controls
    - 21 C.F.R. § 820.80, Receiving, in-process, and finished device acceptance

Suggestions for dealing with device color additives in future

- Evaluation of safety of color additives should be subject to ISO 10993 assessments, just as other chemicals used in medical devices
- FDA should issue a guidance/statement on balancing the risks of using color additives against its benefits (e.g., limiting color additives use to critical human factors issues)
- "Use of …" document needs significant rework
  - Problematic issues not limited to color additives

What about devices already on the market?

- What of 510(k)s and “drift”? No knowledge of whether a color additive was ever used or changed?
- What of PMA devices already on the market with unlisted color additives?
- Public forum needed. Trade associations and individual companies are not the only stakeholders.

Q&A
Discussion

Plan on teaching a color additive course?

Please appropriately acknowledge/reference this Webinar and supporting publications

Brenda Seidman, M.S., Ph.D., RAC

Seidman Regulatory Toxicology, LLC

bcseidman@gmail.com

202-699-1051