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Color Additives and the Medical Device Review

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Webinar Goal

- Describe and clarify ODE's current policy and approach for the evaluation of marketing applications for medical devices that contain color additives (CAs).
- Ensure a consistent approach is being applied to reviews for medical devices that contain CAs

Outline

- Background
- Definitions
- ODE color additives (CA) approach
- When should this approach be used?
- Hierarchical risk-based approach
- Guiding principles for the CA approach
- Detailed CA approach including some examples
- Next steps

Background

- § 721 of the FD&C Act
 - Outlines listing and certification requirements of color additives for foods, drugs, devices and cosmetics:
 - 721(a): a color additive to be used in a device is exempt from listing unless “the color additive comes in direct contact with the body of man or other animals for a significant period of time.”
- ODE does not consider use of a color additive in or on a device to be in contact with the body for a “significant period of time” if the contact duration is 30 days or less.
 - see 721 of the FD&C Act, 21 CFR 70, 21 CFR 71, 21 CFR 73, 21 CFR 74(d), 21 CFR 80



Definitions

Definitions

- **Color Additive (CA)**: “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...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, by regulation, determines is used (or intended to be used) solely for a purpose or purposes other than coloring” (per 201(t) of the FD&C Act)

Definitions (cont.)

- Color Additive (CA) (cont.):

A coloring substance intended for use in a medical device is a color additive under this definition if the substance is capable of imparting color when it is added or applied to the human body. Importantly, a coloring substance in a medical device need not actually impart color to the body from its use in a device to be a color additive.

Definitions (cont.)

- US legally marketed device: refers to any US marketed device (i.e., for 510(k)'s this can refer to either a predicate device or a reference device) which has similar tissue contact (i.e., type and duration).

EXAMPLE:

Coronary balloon angioplasty devices & delivery systems for superficial femoral artery stents could be appropriate reference devices for a CA assessment.

Both contact cardiovascular tissue and blood for < 24 hours (per the G95-1 and ISO 10993-1 approaches).

Definitions (cont.)

- **Direct contact**: term used for a device or device component that comes into physical contact with body tissue
- **Indirect contact**: term used for a device or device component through which a fluid or gas passes, prior to the fluid or gas coming into physical contact with body tissue. In this case the device or device component itself does not physically contact body tissue.
- **Transient contact**: term used for a device or device component that comes into very brief/transient contact with body tissue (e.g., lancets, hypodermic needles, capillary tubes that are used for less than 1 minute)

Definitions (cont.)

- Tolerable Intake (TI): a dose (in mg/kg/day) below which adverse systemic effects are not likely to occur in exposed patients.
 - This dose is not intended to be protective for all adverse effects (e.g., hypersensitivity)
 - The TI is derived using the approach outlined in ISO 10993-17 "Biological evaluation of medical devices - Part 17: Methods for the establishment of allowable limits for leachable substances."

ODE color additives approach

- Based on G95-1, & ISO 10993-1 information (if available), and ODE current practice
- Intended to be risk-based, least burdensome, and scientifically based
- Leverages information already available (i.e., biocompatibility testing of the device in its final finished form)
- Minimizes the need for additional color additive information or extraction studies to look specifically for CA release, where appropriate.

When to use this approach?

- In marketing applications: 510(k)s, PMAs, *de novo* requests, HDEs
- What about IDEs?
 - Not required to initiate IDEs, per §721 of the FD&C Act (21 USC §379e)
 - Caveats:
 - If there is a toxicity risk identified for any chemicals used to manufacture the device (including any color additives), it may be necessary for us to ask for appropriate safety information prior to investigation in humans.
 - Risk based approach to be used.

Hierarchical risk-based approach

- Uses “type/duration of contact categories” outlined in ISO 10993-1 and G95-1
- Different CA information needed for devices/components with:
 - Section I slides: No patient contact (direct or indirect)
 - Section II slides: Less than 24 hour contact
 - Section III slides: 24 hour to 30 day contact
 - Section IV slides: Greater than 30 day contact

Guiding principles (GPs) for the CA approach: GP#1

To determine whether CA information is needed (per GP#7 and GP#8*):

- Use a least burdensome, risk-based approach
- Interpret GP#7 and GP#8 in the appropriate regulatory context (i.e., compared to other similar marketed products).

**GP#7 = descriptive info*

GP#8 = risk assessment info

Guiding principles for the CA approach: GP#2

If your marketing submission is for a:

- New device, or
- Device where the identified US legally marketed comparison device is made by a different manufacturer

Follow the concepts described in slides for Sections I - IV

Guiding principles for the CA approach: GP#3

If you have made a device modification:

- Focus the CA evaluation on:
 - only the device or component modifications
 - unless the change could affect other parts of the device that were not changed
- Provide CA for the impacted portions of the device.

Guiding principles for the CA approach: GP#4

When assessing device modifications:

- Explain why modification is not expected to affect CA release

Types of changes that may affect CA release include:

- material changes
- design changes

Prior testing that may help with assessment:

- Biocompatibility extracts: visual observation of color/turbidity change &/or particulates
- Performance: in vitro particulate or wear testing w/colored particles; or animal studies with colored fragments at explant

Guiding principles for the CA approach: GP#4 (cont.)

Examples of material changes that may affect CA release include:

Changes to: formulation of polymer matrix, CA amount or CA type

Examples of design changes that may affect CA release include:

Changes to: how the CA is incorporated into the patient contacting portion of the device, such as mixed into the polymer vs. stamped on the surface

Guiding principles for the CA approach: GP#5

If device change is not likely to affect release of CA (per available evidence):

- No CA information (per GP#7 or GP#8) is needed.
- Perform biological evaluation:
 - Device in its final finished form (FFF) in accordance with G95-1
 - May include device testing and/or a rationale for why testing was not performed

Guiding principles for the CA approach: GP#6

Contact = intact skin for up to 30 days:

- No CA information (per GP#7 or GP#8) is needed.

For other types of contact up to 30 days:

- CA information may be needed (see slides for Sections II & III).

For contact greater than 30 days, regardless of type of contact:

- CA information (per GP#7, and possibly GP#8) is needed (see slides for Section IV).

Guiding principles for the CA approach: GP#7

If CA information is needed (per Sections II-IV), provide the following:

1. Chemical Name/CAS #
2. Purity information:
 - CFR color listing (e.g., in 21 CFR 73 or 21 CFR 74), or
 - Raw material's Certificates of Analysis (COA), or
 - Raw material or final device testing for impurities;
3. Estimated/calculated maximum amount of each CA (in weight) per device

OR ID: US legally marketed device with same CA, same matrix material, same processing

Guiding principles for the CA approach: GP#7 (cont.)

NOTE: Letters of Authorization from CA manufacturers allowing FDA access to relevant material supplier master files (e.g., MAFs) may be helpful to address the following GP#7 issues:

1. Chemical Name/CAS #
2. Purity information:
 - CFR color listing (e.g., in 21 CFR 73 or 21 CFR 74), or
 - Raw material's Certificates of Analysis (COA), or
 - Raw material or final device testing for impurities;
3. Estimated/calculated maximum amount of each CA (in weight) per device

Guiding principles for the CA approach: GP#8

No additional CA info needed if:

- CA amount is less than or equal to:
 - Comparator device* w/ same CA, same type and duration of tissue contact, same matrix material, & similar intended use; or
- CA/impurity amounts are less than:
 - Tolerable intake (TI) for the CA/impurities

*Prior submissions can be used as comparators, even if prior submissions did not include CA info

Guiding principles for the CA approach: GP#8 (cont.)

Additional CA risk assessment needed if:

- CA amount is greater than: comparator device*
(w/ same CA, same type and duration of tissue contact, same matrix material, & similar intended use)
- CA amount is same or less than comparator, but:
Conditions of device use are not comparable
(tissue/body fluid interface or duration)

GP8:

- | | |
|--|---------------------------|
| - Amt is > TI or Amt in device unknown | - Benefit/risk assessment |
| - Model/determine expected release via elution | - Reduce CA amt? |
| - Amt released > TI | - In vivo fate testing? |
| | - Perhaps a CAP? |

Guiding principles for the CA approach: GP#8 (cont.)

GP8:

- Amt is > TI or Amt in device unknown
- Model/determine expected release via elution
- Amt released > TI
- Benefit/risk assessment
- Reduce CA amt?
- In vivo fate testing?
- Perhaps a CAP?

Examples: Benefit/risk assessment

- Life saving device is used in patients with <1 year life expectancy
- Amount of CA in device is needed for proper placement
- Color/impurity risks (e.g., cancer) don't outweigh benefits

Guiding principles for the CA approach: GP#8 (cont.)

GP8:

- Amt is > TI or Amt in device unknown
- Model/determine expected release via elution
- Amt released > TI
- Benefit/risk assessment
- Reduce CA amt?
- In vivo fate testing?
- Perhaps a CAP?

Examples: Reduce CA amt?

- Reduce the amount of the CA in device to the same or below a US legally marketed device with the same duration and route of exposure (e.g., “appropriate comparator”)
- Reduce exposure to a level corresponding to an acceptable risk in accordance with the risk assessment

Guiding principles for the CA approach: GP#8 (cont.)

GP8:

- Amt is > TI or Amt in device unknown
- Model/determine expected release via elution
- Amt released > TI
- Benefit/risk assessment
- Reduce CA amt?
- In vivo fate testing?
- Perhaps a CAP?

Examples: Other possible options?

- Under certain circumstances (e.g., for colored absorbable devices), conduct in vivo “fate” testing (e.g., absorption, distribution, metabolism, and excretion [ADME]); and/or
- Perhaps submit a color additive petition (CAP), depending on further risk assessment, fate test outcomes, and discussion with CDRH (e.g., Q-submission)

Guiding principles for the CA approach: GP#9

If other CA concerns identified during the review process:

- Review staff to discuss with management whether or not additional testing is needed.
- If you have questions about the CA information requested, contact the review staff and management to discuss.

Detailed CA Approach

Section I: No patient contact*

- No biocompatibility information needed.
- No CA information needed (per GP#7 or GP#8)

**direct or indirect*

Detailed CA Approach

Section II: < 24 hour contact

- a) Contact < 1 minute (transient) & device may release CA:
- Perform biological evaluation:
 - Device in FFF in accordance with G95-1
 - May include device testing and/or a rationale for why testing was not performed
 - No CA information needed (per GP#7 or GP#8), unless performance testing suggests colored material release:

In vitro particulate release testing (e.g., for coated catheters) showing colored particles.

Embolized/migrated colored material in an animal study.

Wear testing demonstrating colored particulate.

Detailed CA Approach

Section II: < 24 hour (cont.)

- b) Contact > 1 minute & device may release CA:
- i. Cytotoxicity, sensitization, and irritation (CSI) tests:
- Performed on device in FFF with acceptable results; AND
 - Extracts: no change in color/turbidity and no visible particulates

Then:

- Perform biological evaluation of the device in FFF per G95-1 (may include other tests and/or rationale for why testing was not performed).
- No CA information needed (per GP#7 or GP#8)

Detailed CA Approach

Section II: < 24 hour (cont.)

- b) (cont.) Contact > 1 minute & device could release CA:
- ii. If CSI tests of the device in FFF:
- NOT performed with acceptable results; OR
 - Performed with acceptable results, but
 - Extracts: change in color/turbidity, and/or visible particulates:

Then

- Perform biological evaluation of the device in FFF per G95-1 (may include other tests and/or rationale for why testing was not performed).
- CA (per GP#7); AND Risk Assessment (per GP#8) needed

Detailed CA Approach

Section II: < 24 hour (cont.)

b) (cont.) Contact > 1 minute & device could release CA:

GP7:

- | | |
|--|--|
| <ul style="list-style-type: none"> - Chemical name/CAS#; - Purity info; <u>and</u> - Max amount of each CA (in wt)/device | <p>OR</p> <ul style="list-style-type: none"> - Identification of US marketed device w/same CA, matrix, processing |
| <ul style="list-style-type: none"> - If CA amount <u>less than or equal to</u> appropriate* comparator, OR <u>less than</u> TI - No CA information (per GP#8) needed | |

GP8:

- | | |
|---|--|
| <ul style="list-style-type: none"> - Amt is > TI or Amt in device unknown - Model/determine expected release via elution - Amt released > TI | <ul style="list-style-type: none"> - Benefit/risk assessment - Reduce CA amt? - In vivo fate testing? - Perhaps a CAP? |
|---|--|

Detailed CA Approach

Section III: 24 hour–30 day use*

If device may release CA:

- i. Cytotoxicity, sensitization, and irritation (CSI) tests:
 - Performed on device in FFF with acceptable results; AND
 - Other G95-1 biocomp tests: Performed on device in FFF w/acceptable results
 - Extracts: no change in color/turbidity and no visible particulates

Then: No CA information needed (per GP#7 or GP#8)

** Includes repeat use equivalent to 24 hours up to 30 days. For example, an inhaler used daily, may be intended for use with a medication that is prescribed for two weeks, so the assessment should be conducted using this 24 hr to 30 day category.*

Detailed CA Approach

Section III: 24 hour–30 day use*

If device may release CA:

- i. Cytotoxicity, sensitization, and irritation (CSI) tests:
 - Performed on device in FFF with acceptable results; AND
 - Other G95-1 biocomp tests: Performed on device in FFF w/acceptable results
 - Extracts: no change in color/turbidity and no visible particulates

Then: No CA information needed (per GP#7 or GP#8)

** Includes repeat use equivalent to 24 hours up to 30 days. For example, an inhaler used daily, may be intended for use with a medication that is prescribed for two weeks, so the assessment should be conducted using this 24 hr to 30 day category.*

Detailed CA Approach

Section III: 24 hr–30 d (cont.)

- ii. (cont.) For biocomp tests of the device in FFF, if:
- CSI Tests: NOT performed with acceptable results; OR
 - Other G95-1 biocomp tests: Not performed w/acceptable results; OR
 - All tests performed with acceptable results, but
 - Extracts: change in color/turbidity, and/or visible particulates:

Then

- Perform biological evaluation of the device in FFF per G95-1 (testing and/or rationale).
- CA info (per GP#7); AND Risk Assessment (per GP#8) needed

Detailed CA Approach

Section III: 24 hr–30 d (cont.)

EXAMPLE 1: Multi-day infusion catheter

- CSI: performed on device in FFF w/ acceptable results ✓
- Other G95-1 tests: performed w/acceptable results ✓
- Extracts (all tests): no change in color/turbidity, and no visible particulates ✓

Then: No CA info needed (per GP#7 or GP#8)

Detailed CA Approach

Section III: 24 hr–30 d (cont.)

EXAMPLE 2: Multi-day infusion catheter

- Cytotoxicity & Sensitization: performed on device in FFF w/ acceptable results ✓
- Irritation testing showed slight toxicity
- Other G95-1 tests: performed w/acceptable results ✓
- Extracts (all tests): no change in color/turbidity, and no visible particulates ✓

Then: CA info (per GP#7); AND Risk Assessment (per GP#8) needed

Detailed CA Approach

Section III: 24 hr–30 d (cont.)

EXAMPLE 3: Multi-day infusion catheter

- CSI: performed on device in FFF w/ acceptable results ✓
- No genotoxicity testing on device in FFF provided
- Other G95-1 tests: performed w/acceptable results ✓
- Extracts (all tests): no change in color/turbidity, and no visible particulates ✓

Then: CA info (per GP#7); AND Risk Assessment (per GP#8) needed

Detailed CA Approach

Section III: 24 hr–30 d (cont.)

EXAMPLE 4a: Multi-day infusion catheter

- CSI: performed on device in FFF w/ acceptable results ✓
- Other G95-1 tests: performed w/acceptable results ✓
- Extracts (one test): no change in color/turbidity, but visible particulates present

Then: CA info (per GP#7); AND Risk Assessment (per GP#8) needed

Detailed CA Approach

Section III: 24 hr–30 d (cont.)

EXAMPLE 4b: Multi-day infusion catheter

- CSI: performed on device in FFF w/ acceptable results ✓
- Other G95-1 tests: performed w/acceptable results ✓
- Extracts (one test): no change in color/turbidity, but visible particulates present*

Then: CA info (per GP#7); AND Risk Assessment (per GP#8) needed

**CAVEAT: If info is provided to confirm the source of particulates is not from leaching of CA during biocompatibility extraction studies (e.g., images to document particulates are cutting artifacts that occur prior to extraction, chemical identification of particulates), CA information (per GP#7 or GP#8) is not needed.*

Detailed CA Approach

Section III: 24 hr–30 d (cont.)

ii. (cont.)

GP7:

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|--|--|
| <ul style="list-style-type: none"> - Chemical name/CAS#; - Purity info; <u>and</u> - Max amount of each CA (in wt)/device | <p>OR</p> <ul style="list-style-type: none"> - Identification of US marketed device w/same CA, matrix, processing |
| <ul style="list-style-type: none"> - If CA amount <u>less than or equal to</u> appropriate* comparator, OR <u>less than TI</u> - No CA information (per GP#8) needed | |

GP8:

- | | |
|---|--|
| <ul style="list-style-type: none"> - Amt is > TI or Amt in device unknown - Model/determine expected release via elution - Amt released > TI | <ul style="list-style-type: none"> - Benefit/risk assessment - Reduce CA amt? - In vivo fate testing? - Perhaps a CAP? |
|---|--|

Detailed CA Approach

Section IV: > 30 day use*

If the device may release CA:

- Perform biological evaluation of the device in its FFF per G95-1 (testing and/or rationale); AND
- CA information (per GP#7); AND Risk Assessment per (GP#8) needed

**Includes repeat use beyond 30 days. For example, hemodialyzers are used for approximately 3 hours at a time, but can be used multiple times per week, and for more than 30 days; therefore, the assessment should be conducted using this >30 day category.*

Detailed CA Approach

Section IV: > 30 day use (cont.)

(cont.)

GP7:

- | | |
|--|--|
| <ul style="list-style-type: none"> - Chemical name/CAS#; - Purity info; <u>and</u> - Max amount of each CA (in wt)/device | <p>OR</p> <ul style="list-style-type: none"> - Identification of US marketed device w/same CA, matrix, processing |
| <ul style="list-style-type: none"> - If CA amount <u>less than or equal to</u> appropriate* comparator, OR <u>less than TI</u> - No CA information (per GP#8) needed | |

GP8:

- | | |
|---|--|
| <ul style="list-style-type: none"> - Amt is > TI or Amt in device unknown - Model/determine expected release via elution - Amt released > TI | <ul style="list-style-type: none"> - Benefit/risk assessment - Reduce CA amt? - In vivo fate testing? - Perhaps a CAP? |
|---|--|

Other Considerations

- If devices with different types & amounts of colors (e.g., contact lenses) are being proposed:
 - A device sample incorporating all colors could be used for biocompatibility testing.
- If a device is offered in a range of shades of a particular color (e.g., colored dental composite resins):
 - The device with the most CAs could be used for biocompatibility testing.

Summary: ODE CA approach

- Based on G95-1, & ISO 10993-1 information (if available), and ODE current practice
- Intended to be risk-based, least burdensome, and scientifically based
- Leverages information already available (i.e., biocompatibility testing of the device in its final finished form)
- Minimizes the need for additional color additive information or extraction studies to look specifically for CA release, where appropriate.



Next Steps

- Future Draft Level 1 Guidance planned for color additives in medical devices

Questions?

General questions about the use of color additives in medical devices? Contact - Division of Industry and Consumer Education: DICE@fda.hhs.gov (800) 638-2041

Questions about use of color additives in a specific device?
Contact - Jennifer Goode: jennifer.goode@fda.hhs.gov
(301) 796-6374

Slide Presentation, Transcript and Webinar Recording will be available at: <http://www.fda.gov/training/cdrhlearn>

Under Heading: Specialty Technical Topics