

ChloroPrep® with Tint

Three-Year Exclusivity and Related Issues

Medi-Flex, Inc.



Discussion Items

1. Background about the product and its three-year exclusivity
2. Medi-Flex's study of the tint ingredient was a required clinical trial
3. Tint study covers Cardinal's product
4. Cardinal's ANDA is improper



Item 1: Background

- Product at issue is ChloroPrep[®] with Tint (chlorhexidine gluconate 2%, isopropyl alcohol 70%)
 - Over-the-counter topical sponge
 - Used as an antiseptic for surgical preparation
- Medi-Flex was the first company to develop this product for this indication
 - Medi-Flex submitted NDA 20-832 in 1997 for the original untinted ChloroPrep[®] One-Step product
 - Approved in 1.5 ml, 3 ml, and 10.5 ml applicators



Background (cont.)

- Medi-Flex developed two innovations to ChloroPrep[®] One-Step
 - Added a tint ingredient (FD&C Green No. 3)
 - Allows users to see treated areas to facilitate application
 - Helps to prevent pooling and reduce fire risk
 - Increased the applicator volume to 26 ml
- NDA supplement for ChloroPrep[®] with Tint
 - FDA required two clinical trials for approval
 - Efficacy study to support the tint ingredient
 - Safety study to support the increased applicator volume



Background (cont.)

- ChloroPrep[®] with Tint in a 26 ml volume was approved on May 3, 2005
 - Received three-year exclusivity
 - Covered by a patent directed to tinted products
 - 8 years after the original ChloroPrep[®] One-Step NDA
- Cardinal now seeks approval of a generic version of ChloroPrep[®] with Tint
 - Different FD&C color (Red No. 40)
 - 10.5 ml applicator volume
 - Cardinal's ANDA relies on untinted ChloroPrep[®] One-Step
 - ChloroPrep[®] with Tint was not approved when Cardinal submitted its ANDA



Issues

- FDA should not approve Cardinal's ANDA for a tinted product because the ANDA is blocked by Medi-Flex's three-year exclusivity
- Two options with respect to Cardinal's improper ANDA
 - Cardinal should change the RLD to ChloroPrep® with Tint, or
 - Cardinal should submit its own clinical data similar to Medi-Flex under a 505(b)(2) application



Item 2: Medi-Flex's Tint Study was a Required Clinical Trial

- FDA identified the tint study as a required clinical trial in its exclusivity summary
- Approval history shows that FDA required a clinical trial to prove that the tint does not affect efficacy
- The tint study was specifically designed as an efficacy study under the Tentative Final Monograph for Antiseptic Products (TFM)
- Similar TFM studies for Chloraprep[®] One-Step resulted in exclusivity



FDA's Exclusivity Summary

- Pages 5 and 6 of FDA's exclusivity summary identify the efficacy study regarding the tint and the safety study regarding the increased applicator as new clinical investigations essential to approval
 - The tint study is titled "Clinical Simulation Study Test for Pre-Operative Skin Preparation"
 - The increased applicator study is titled "Evaluation of the Area Covered by a Pre-Operative Skin Preparation"



Approval History of ChloroPrep[®] With Tint

- March 11, 2003 – CBE30 supplement for untinted 26 ml product
- April 9, 2003 – CBE30 unacceptable for filing because clinical data is required
- July 6, 2004 – Prior Approval Supplement (PAS) for the tinted 26 mL product
- Nov. 5, 2004 – PAS unapprovable because clinical data required
 - Efficacy study regarding the addition of the tint ingredient
 - Safety study regarding the 26 ml applicator volume
- Dec. 31, 2004 – Safety and efficacy data submitted
- May 3, 2005 – PAS approved with three-year market exclusivity
- May 6, 2005 – CBE30 supplement submitted for tinted 10.5 ml
- April 3, 2006 – CBE30 supplement approved for tinted 10.5 ml



Tint Study is an Efficacy Study

- Purpose of study was to “evaluate the antimicrobial effectiveness potential”
 - Conducted utilizing TFM methodology
 - 3.0 log₁₀ reduction in CFU/cm² of skin on groin sites within 10 minutes
 - 2.0 log₁₀ reduction of skin on abdomen sites within 10 minutes
- Approximately 60 subjects with 16 test areas
- ChloroPrep[®] with Tint was a test product and povidone-iodine was the control product



Similar Studies for ChloroPrep® One-Step Received Exclusivity

- NDA 20-832 – Approved July 14, 2000
 - Efficacy testing required for approval utilized similar TFM methodology
 - Market exclusivity expired July 14, 2003
- NDA 21-555 – Approved October 7, 2002
 - Efficacy testing required for approval utilized similar TFM methodology
 - Market exclusivity expired October 7, 2005



Item 3: Cardinal's Product Incorporates Medi-Flex's Innovation

- Innovation of ChloraPrep® with Tint
- Review of FD&C tints, chlorhexidine, and isopropyl alcohol
- Medi-Flex studied the same problem inherent in Cardinal's product



Innovation: ChloroPrep® with Tint

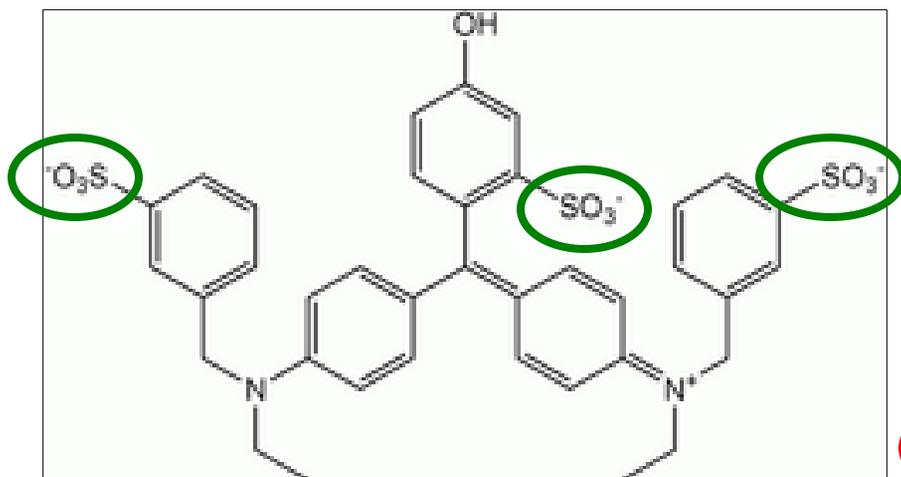
- Medi-Flex developed a successful tinted formulation
 - Contains chlorhexidine (CHG), isopropyl alcohol (IPA), and tint
- 2% CHG in 70% IPA = ChloroPrep®
- Tint ingredient provides better visualization
 - Facilitates effective application
 - Helps to prevent pooling and reduce fire risk



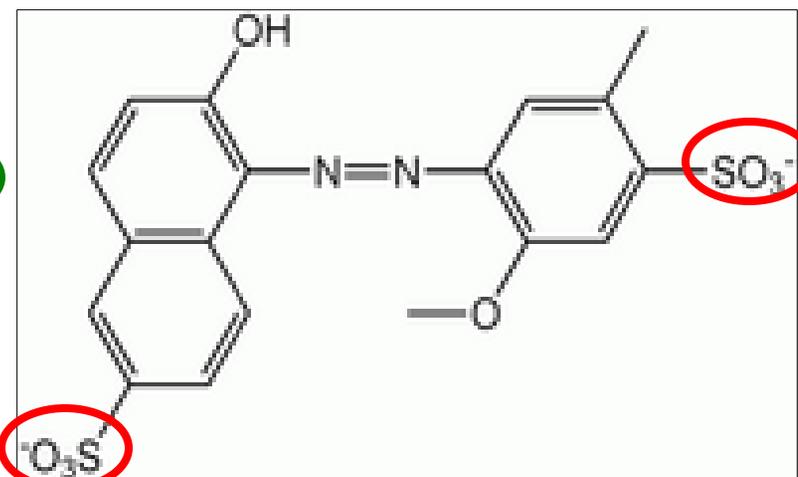
Review of FD&C Tints

- FD&C Tints
 - Anionic
 - High water solubility
 - Bulky aromatic salts
 - Provide color to facilitate application of chlorhexidine products

Green No. 3 & Red No. 40 are Anionic in Solution



FD&C Green No. 3



FD&C Red No. 40



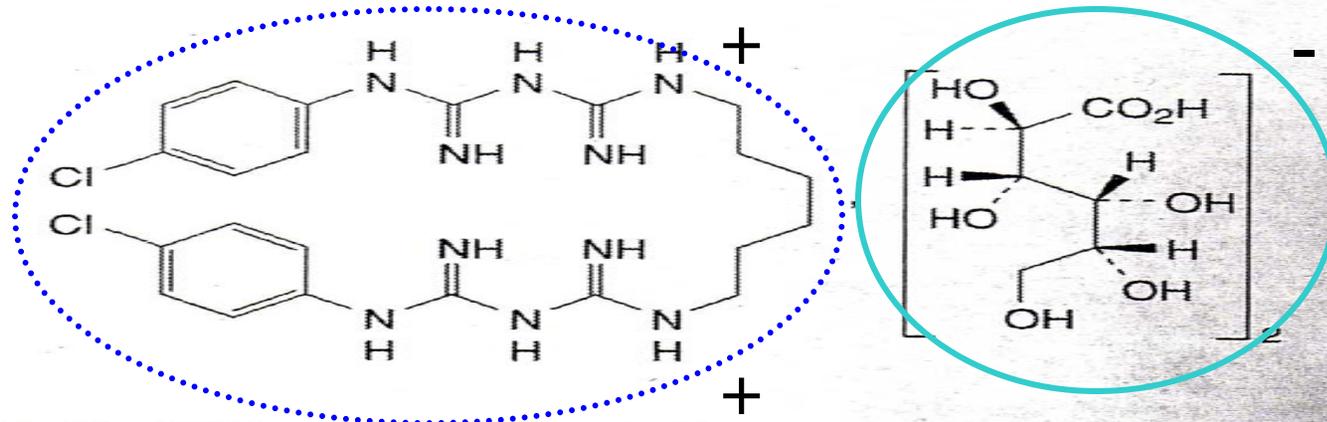
Review of Chlorhexidine

- Chlorhexidine
 - Cationic
 - Broad based antibacterial
 - Known to bind with anionic FD&C dyes
 - Clear in solution
 - Difficult to formulate

Chlorhexidine is Cationic

Chlorhexidine Gluconate Solution

(Ph Eur monograph 0658)



$C_{22}H_{30}Cl_2N_{10}, 2C_6H_{12}O_7$ 898

18472-51-0

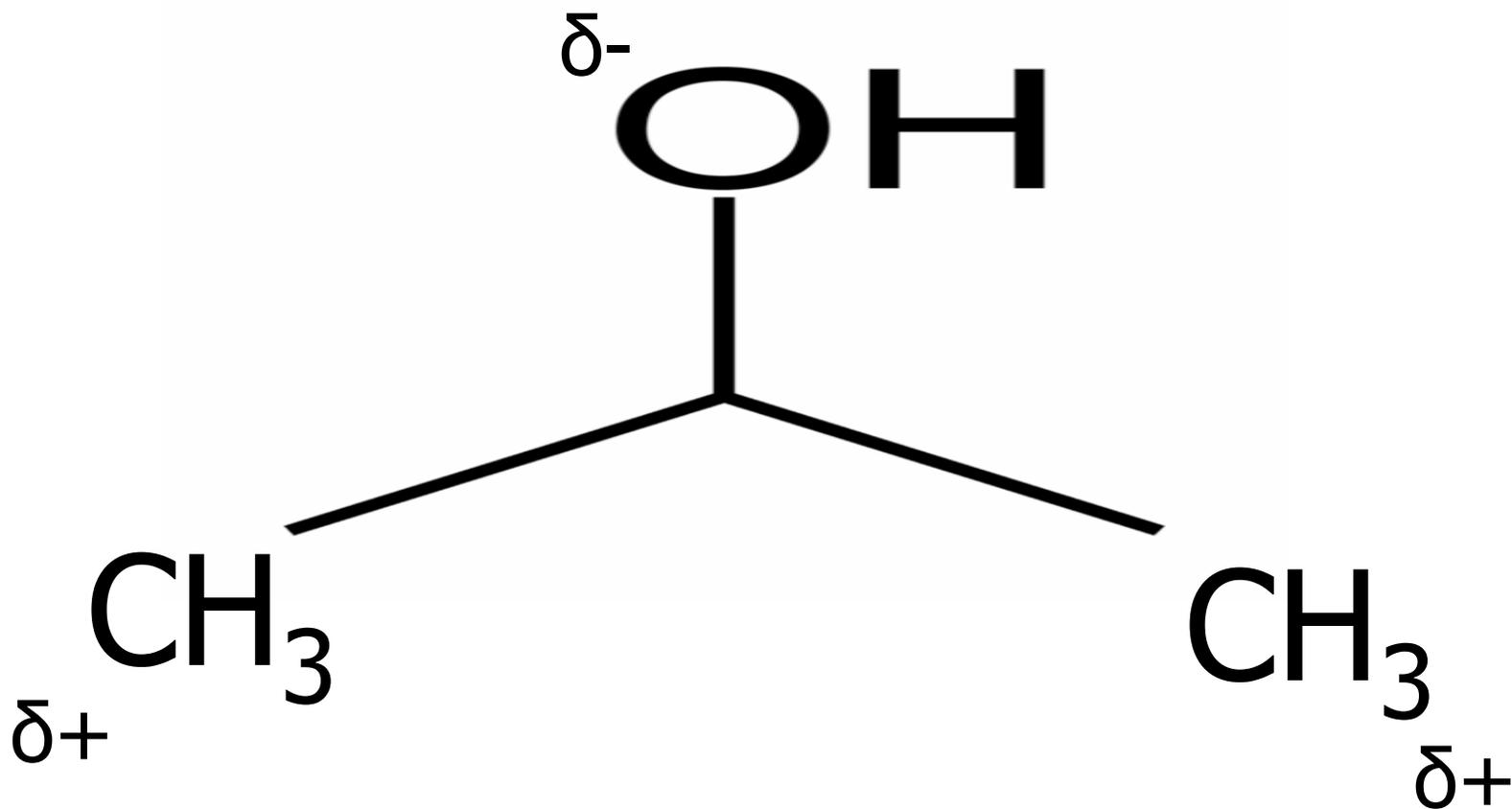
Ph Eur



Review of Isopropyl Alcohol

- Isopropyl alcohol
 - Polar
 - Organic character
 - Provides solubility vehicle for the tint
 - Stabilizes the tint ingredient
 - Not simply a second active ingredient
 - Polar nature shields the cationic chlorhexidine from the anionic tint (regardless of the tint color)
 - Without IPA, the tint and chlorhexidine form a precipitant

Isopropyl Alcohol is Polar





Medi-Flex Studied the Same Problem Inherent in Cardinal's Product

- Ionic interactions limit anionic dye solubility with CHG
- The anionic dye may affect the cationic CHG
- Medi-Flex's study used a formulation containing CHG, IPA, and an FD&C anionic tint (Green No. 3)
- Cardinal has the same formulation
 - Except uses a different FD&C anionic tint (Red No. 40)
 - Same anionic property
 - Same empirical behavior (Tinted 2% CHG in 70% IPA)
- Same problem studied by Medi-Flex exists with Cardinal's product
 - Medi-Flex's study confirmed that an anionic tint does not affect the cationic CHG in the presence of the polar IPA



Item 4: Improper ANDA

- Cardinal should have originally submitted a 505(b)(2) application
- FDA should require Cardinal to reference a tinted RLD or use a 505(b)(2) because the tint requires clinical data
- The tinted and untinted products are not therapeutically equivalent
- Cardinal's ANDA circumvents Medi-Flex's patent contrary to the Hatch-Waxman Act
- Creates labeling concerns



Cardinal Should Have Originally Submitted a 505(b)(2) Application

- Cardinal should not have submitted an ANDA relying on the untinted RLD
- Cardinal added a tint ingredient to the RLD
- Addition of a tint requires clinical data
 - FDA required Medi-Flex to conduct a clinical trial
 - Arbitrary and capricious to apply a higher standard of approval to Medi-Flex
- Clinical data is inappropriate for an ANDA
 - Cardinal should have originally submitted a 505(b)(2) application with clinical data



FDA Should Require Cardinal to Reference a Tinted RLD or Use a 505(b)(2)

- Cardinal should use ChloroPrep® with Tint as RLD
 - Cardinal may rely on Medi-Flex's tint data with this RLD
 - FDA has authority to require Cardinal to change
 - ChloroPrep® with Tint in a 10.5 ml volume (same as Cardinal) was approved in April 2006
 - Specifically designated by FDA as the RLD
- Alternatively, Cardinal should file a 505(b)(2)
 - Cardinal may perform its own study like Medi-Flex
 - Not a limited confirmatory study that could be in an ANDA



Not Therapeutically Equivalent

- Products are not therapeutically equivalent
 - Fundamentally different products
 - Not interchangeable in a clinical setting
 - Tint provides safety and efficacy function
 - Effective application by showing previously treated areas
 - Safe application by reducing pooling and fire risk
 - Generic word "Tint" is part of FDA approved trade name
 - Provides important functional role
 - Labeling issues



Contrary to the Hatch-Waxman Act

- Cardinal is effectively circumventing Medi-Flex's patent directed to tinted products
 - Medi-Flex has a patent on tinted products
 - Could not list the tint patent with untinted RLD
 - Cardinal's tinted ANDA relied on the untinted RLD
 - Did not have to certify to the tint patent
 - Contrary to the Hatch-Waxman Act
 - Cardinal should not have used the untinted RLD
 - Cardinal should be required to certify to the patent



Labeling Issues

- Cardinal's use of the untinted RLD creates labeling concerns
 - Cardinal's labeling will be similar to the untinted ChloroPrep® One-Step
 - Will likely include the phrase "One-Step"
 - Confusion with untinted ChloroPrep® One-Step
 - Will not indicate product is tinted
 - Potentially misleading



Summary

- Medi-Flex's Exclusivity Blocks Cardinal's Product
 - Medi-Flex developed a successful chlorhexidine formulation containing an anionic FD&C tint and isopropyl alcohol
 - FDA required Medi-Flex to study the tinted formulation
 - Medi-Flex's study confirmed that ionic interactions protect the cationic chlorhexidine from the anionic tint
 - Cardinal has the same formulation except uses a different anionic FD&C tint
 - Medi-Flex's study and exclusivity cover Cardinal's product
- Cardinal filed an improper ANDA
 - FDA should require Cardinal to reference ChloroPrep® with Tint as the RLD or submit a 505(b)(2) application