Regulation of Health Care Antiseptics

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August 30, 2022

The opinions and information in this presentation are my own and do not reflect the views and policies of the FDA

Categories of OTC Antiseptics

- Consumer Antiseptics
  - Rubs (leave-on products)
    - Hand rubs
      "hand sanitizer"
    - Antiseptic hand wipes
  - Washes
    - Hand wash
      "antibacterial soap"
    - Antibacterial body wash
- First Aid Antiseptics
- Health Care Antiseptics
  - Health care personnel hand wash
  - Health care personnel hand rub
  - Surgical hand scrub
  - Surgical hand rub

Patient preoperative skin preparation

- Food Handler Antiseptics

Regulatory Pathway for Marketing Nonprescription Drugs

- New Drug Application/Abbreviated New Drug (NDA/ANDA)
  - Application submitted to FDA for premarket approval
- OTC Drug Review (OTC Monograph)
  - Marketed without an approved drug application if the drug complies with statutory and regulatory requirements
  - Began in 1972 to evaluate the safety and effectiveness of OTC drug products marketed in the United States before May 11, 1972
  - Established conditions under which an OTC drug is generally recognized as safe and effective (GRASE) in the form of OTC monographs

OTC Drug Monograph

- A “rule book” for each therapeutic category establishing conditions, such as active-ingredients, uses (indications), doses, route of administration, labeling, and testing under which an OTC drug is generally recognized as safe and effective (GRASE)

- OTC monographs cover ~ 800 active ingredients for over 1,400 different uses, authorizing over 100,000 drugs

Two Regulatory Pathways

New Drug Application	Over The Counter (OTC) Monograph
Product specific (including formulation and labeling)	Therapeutic category-specific (product can contain permissible active ingredients in a monograph compliant formulation)
Certain subsequent labeling and formulation changes require prior approval through supplemental application	Changes do not require approval when in compliance with the monograph
Confidentiality during the approval process	Generally, a public process for monograph changes
Safety and effectiveness testing required for each individual product	Safety and effectiveness testing of each individual product not required if compliant with monograph
Each product requires premarket approval via a New Drug Application (NDA/ANDA)	Changes to monograph require premarket approval via an OTC Monograph Order Request (OMOR)
Application fees (i.e., user fees)	Application fees (i.e. user fees) lower than NDA
Adverse event and other reporting requirements	Limited reporting requirements (serious adverse events only)
Comply with good manufacturing practices	Comply with good manufacturing practices
A period of market exclusivity (if certain conditions are met)	A period of market exclusivity (if certain conditions are met)

Patient Preoperative Skin Preparation Active Ingredients

NDA[1]	Monograph[2]
• Chlorhexidine gluconate (CHG)	• Alcohol (ethanol) • Povidone iodine • Benzalkonium chloride • Isopropyl alcohol • Benzethonium chloride • Chloroxylenol

[1] May also contain other ingredients

[2] Combination products not permitted

Health Care Antiseptics Under OTC Monograph Reform

- On March 27, 2020, the President signed into law H.R. 748, the "Coronavirus Aid, Relief, and Economic Security Act" (CARES Act) which modernizes the OTC drug review
- Healthcare antiseptics using certain active ingredients may be marketed under Section 505G(a)(3) if they follow the 1994 Antiseptics TFM, as further amended by the 2015 Health Care Antiseptics proposed rule[1], and other applicable requirements (e.g. CGMP)

[1]"Topical Antimicrobial Drug Products for Over-the-Counter Human Use; Tentative Final Monograph for Health-Care Antiseptic Drug Products," Proposed Rule, 59 FR 31402 (June 17, 1994) (1994 TFM) as further amended by "Safety and Effectiveness of Health Care Antiseptics; Topical Antimicrobial Drug Products for Over-the-Counter Human Use; and Proposed Amendment of the Tentative Final Monograph; Reopening of Administrative Record," Proposed Rule, 80 FR 25166 (May 1, 2015)

Health Care Antiseptics Under OTC Monograph Reform (Continued)

- Active ingredients **require additional data** to determine whether they are Generally Recognized as Safe and Effective (GRASE) for use in healthcare antiseptics
- It is the manufacturer's responsibility to ensure their products
  - have been properly tested
  - comply with all applicable regulations
  - have inactive ingredients that are safe and suitable for use in an OTC healthcare antiseptic

Patie nt Preoperative Skin Preparation Example Indication and Labeling[1]

Indication

- To help reduce bacteria that can potentially cause skin infection
- For preparation of the skin prior to surgery

Directions

- For external use only
- Clean the area. Apply product to the operative site prior to surgery
- Allow to dry completely; do not rinse

Key warnings

- Not sterile
- Discontinue use if irritation and redness develops
- Keep out of eyes, ears, and mouth
- Do not use
  - With electrocautery procedures (IPA only)
  - On patients with known allergies
  - For lumbar punctures or in contact with the meninges (CHG only)
  - On open skin wounds or as a general skin cleanser

[1] Not an all-inclusive list; individual product labels may differ. Claims are expected to conform to "Topical Antimicrobial Drug Products for Over-the-Counter Human Use; Tentative Final Monograph for Health-Care Antiseptic Drug Products," Proposed Rule, 59 FR 31402 (June 17, 1994).

Patient Preoperative Skin Preparation Safety and Efficacy Testing

- Testing based on labeled indication and use
  - Reduction of bacteria on the skin that potentially can cause skin infection
  - For preparation of the skin prior to surgery (intact skin)
- Includes in vitro and clinical simulation testing for efficacy
- Does not test for
  - Viruses
  - Reduction of systemic infection or specific infections
  - Repeated use
  - Use over large surface area, such as bathing
  - Use in infants/neonates
  - Use in eyes, ears, nose, mouth, vagina, open wounds, etc.
  - Use for pre-catheterization

In Vitro Efficacy Studies

- Designed to demonstrate the product's spectrum and kinetics of antimicrobial activity
- Determination of the in vitro spectrum of activity against recently isolated normal flora and cutaneous pathogens
- MIC or MBC testing of 25 representative clinical isolates and 25 ATCC reference strains
- Time kill testing of each of the microorganisms tested in MIC/MBC

59 FR 31402 at 31444

Clinical Simulation Efficacy Studies

- Based on a surrogate endpoint (*i.e.,* number of bacteria removed from the skin), rather than a clinical outcome (*e.g.,* reduction in the number of infections)
- Evaluates a single application of the product on a dry skin site (abdomen or back) and a moist skin site (groin or axilla) with higher numbers of resident bacteria (59 FR 31402 at 31450)
- Compares test product to vehicle (negative) control and positive control
  - Superiority margin of 1.2 $\log_{10}$ reduction over negative control on abdomen and groin after 30 seconds or 10 minutes
  - Does not exceed baseline at 6 hours
- Limited data directly linking surrogate to clinical outcomes; placebo-controlled outcome studies unethical due to high risk of serious outcomes

FDA Resources

- For Questions on
  - Hand sanitizers COVID-19-HandSanitizers@fda.hhs.gov
  - OTC Monograph Reform druginfo@fda.hhs.gov
  - Small business and industry assistance cdersbia@fda.hhs.gov
  - Registration and listing edrls@fda.hhs.gov
- Resources
  - Methanol and Hand sanitizers consumers should not use www.fda.gov/unsafehandsanitizers
  - Healthcare antiseptics https://www.fda.gov/drugs/information-drug-class/topical-antiseptic-drug-products


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