CENTER FOR DRUG EVALUATION AND RESEARCH

Antiviral Claims and OTC Hand Antiseptics

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Petition to Include Antiviral Claims on OTC Hand Antiseptics
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- **Amend the 1994 TFM**
- **Antiviral labeling for hand antiseptics**
  - General antiviral claim for
    - Consumer
    - food handler
    - healthcare personnel hand antiseptic products
- **For products that meet the criteria for antibacterial claims**
- **Dosage forms not specified**

Petition's proposal

- **Antiviral claims allowed on products that:**
  - Can demonstrate a specified reduction in viral titer
  - Against a respiratory and an enteric viral surrogate
  - Using voluntary consensus methods
- **Claims**
  - General claim-no specific viruses in labeling
    - Antiviral statement of identity
    - Decreases viruses that potentially cause disease

Petition's Proposed Testing Requirements

- **Effectivness criteria**
  - 2 $\log_{10}$ reduction in viral titer compared to a standard hard water control
- **ASTM methods**
  - ASTM E 1838-96 (finger pad method)
  - ASTM E 2011-99 (entire hand method)
- **Surrogate viruses**
  - Rotavirus Wa (ATCC) strain VR-2018)
  - Rhinovirus Type 37 (ATCC strain VR- 1147) or Rhinovirus Type 14 (ATCC strain VR-284

Justification - Antiviral claims on OTC hand antiseptics

- **Prevalence of viral diseases**
- **Importance of hand transmission in the development of viral disease**
- **Current OTC antiseptics have demonstrated antiviral activity**
  - chlorhexidine gluconate, chloroxylenol, ethanol, isopropyl alcohol, quaternary ammonium compounds, and triclosan
    - clinical outcome studies
    - *in vivo* clinical simulation studies (finger pad and whole hand)
    - *in vitro* tests (suspension and carrier)

Justification - Use of viral surrogates

- **No "sentinel species" of virus to serve as the least susceptible to inactivation**
- **Rotavirus and Rhinovirus**
  - important human respiratory and enteric pathogens
  - shown to survive on skin and environmental surfaces
  - Both are nonenveloped viruses that are resistant to inactivation by surfactants alone and represent a stringent test of antiseptic effectiveness
  - broad laboratory experience with the proposed viruses

Justification - Test Methods and Criteria

- **ASTM methods**
  - Provide a reproducible measurement of effectiveness
  - Have been conducted using a variety of active ingredients with a variety of different organisms
- **Effectiveness criteria**
  - based on $\log_{10}$ reductions for alcohol obtained in clinical simulation studies
  - higher than $\log_{10}$ reductions for water or soap and water

FDA Response - Standards of Effectiveness of OTC Drugs

- **21 CFR 330.10(b) defines adequate and well controlled effectiveness studies**
  - capable of distinguishing drug effect from other influences such as a spontaneous change in the course of the disease, placebo effect, or biased observation
  - includes controls that are adequate to provide an assessment of drug effect
  - Adequate measures to minimize bias
  - adequate analysis methods to demonstrate effectiveness

FDA Evaluation – Clinical Effectiveness

- **Data are not sufficient to demonstrate the effectiveness of OTC antiseptics against viruses**
- **Clinical outcomes studies**
  - not adequately controlled to distinguish the effect of antiseptic products from other influences
  - Not adequately designed to minimize bias
  - Inadequate statistical analysis
- **In vivo clinical simulation studies**
  - Soap and water found be as effective or more effective than the antiseptic

FDA Evaluation – In Vitro Effectiveness

- Not predictive of clinical effectiveness
- Many studies did not meet current standards for adequately controlled *in vitro* assays of viral inactivation
- Lacked sufficient detail

FDA Evaluation – Proposed Testing Surrogate Viruses

- Wide range of viral susceptibility to antiseptics makes extrapolation difficult
- Relevance to use requested use settings
- Products making general antiviral claims should be able to demonstrate the widest possible spectrum of activity after a brief contact time
- Other relevant viruses that may be equally susceptible or more resistant to a number of antiseptics

FDA Evaluation – Proposed Testing Effectiveness Criteria

- Data are not sufficient to establish a clinically relevant reduction in viral titer
- Proposed 2-log reduction may not be relevant to many viruses
- Data from clinical outcome studies are needed to identify a clinically relevant effectiveness criteria

FDA Evaluation – Proposed Testing ASTM Methods

- **Good starting point**
- **Needs to address variable of product use**
  - Contact time
  - Organic load
- **Not indicative of effectiveness against a broad range of viruses**
  - Suspension testing may address this concern
- **Design concerns**
  - Protocols not adequate to account for the variability of the data
  - Don't provide guidance on powering the study or analysis of data
- **Will need to establish an active control capable of validating study conduct**

FDA evaluation – Proposed Testing ASTM-1838-02 (Finger Pad Method)

- **May be unreliable for enveloped viruses**
- **Sampling will need to be standardized**
- **Does not reflect product actual use conditions**
- **Does not address neutralization of antiseptic**
- **Does not have controls necessary for a viral assay**
  - Cell control
  - Viral susceptibility and infectivity
  - Cytotoxicity
  - Neutralizer validation

FDA Evaluation – Proposed Testing ASTM 2011-09 (Whole Hand Method)

- Potential for virus wash-off during the pre- and post-treatment tap water rinse
- Only a small of the contaminated area is sampled
- Volume of recovery medium is too large to allow for detection of virus without a concentration step
- High virus stock preparations increase the probability of aggregate formations
- Paper towel-drying step makes it difficult to account for the true extent of virus elimination

FDA Recommendations for Data

- **Adequate and well controlled clinical trials in each of the requested use settings**
- **In vitro studies to define key aspects of virus inactivation**
  - Viral susceptibilities to antiseptic against geographically and temporally distinct isolates
  - Effective concentration or range of concentrations
  - Kinetics of viral inactivation
  - Effect of environmental factors

Questions?

Back up slides

Scope of 1994 TFM

- **Hospital antiseptic**
  - Healthcare personnel handwashes
  - Patient preoperative skin preparations
  - Surgical hand scrubs
- **Consumer antiseptic handwashes**
- **Active ingredients**
  - Alcohols
  - Povidone-iodine
- **Labeling**
- **Final formulation testing**

Data required for antibacterial effectiveness 1994 TFM

- **In vitro**
  - Spectrum of activity
  - Kinetics of activity
  - Resistance
- **In vivo**
  - Clinical simulation studies mimicking actual use conditions
  - Effectiveness criteria
    - Log reduction
    - Not validated
    - Extensive history of use of this standard in the approval of hospital products

1994 TFM – Proposed Labeling of OTC Hand Antiseptics

- **No reduction in infection claims**
- **No listing of specific organisms**
- **Reduction of bacteria on the skin**
- **Directions for use based on the results of final formulation testing**
  - Application times
  - Number of applications