

Antiviral Claims and OTC Hand Antiseptics

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Petition to Include Antiviral Claims on OTC Hand Antiseptics January 2003

- 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 log₁₀ 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 log₁₀ reductions for alcohol obtained in clinical simulation studies
- higher than log₁₀ 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)

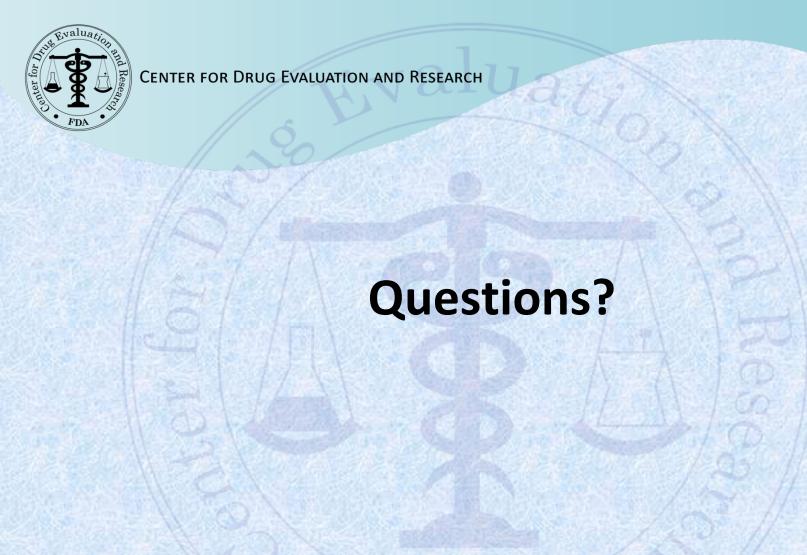
- May be unreliable for enveloped viruses
- Sampling will need to be standardized
- Does not reflect product actual use conditions
- Does not address neutralization of antiseptic
- Does not have controls necessary for a viral assay
 - Cell control
 - Viral susceptibility and infectivity
 - Cytotoxicity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

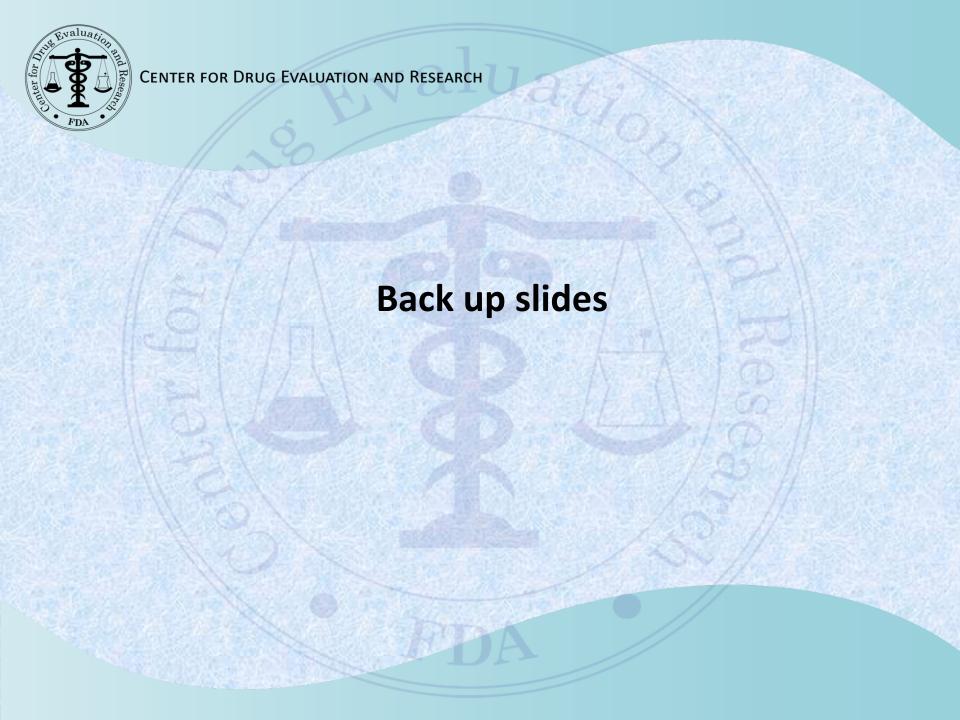
FDA Evaluation – Proposed Testing ASTM 2011-09 (Whole Hand Method)

- 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





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