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

- **Effectiveness 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
    - \textit{in vivo} clinical simulation studies (finger pad and whole hand)
    - \textit{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