
Regulatory Issues in Clinical Effectiveness Trials

Report from WHO meeting on “Scientific Basis for Regulatory Decisions on Microbicides”, 4-6 March 2002, Villars-sur-Olon, Switzerland

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Acknowledgments

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Objective

- To identify minimal requirements for demonstrating sufficient clinical effectiveness of vaginal microbicides to support licensure
- Discussion was limited to first generation microbicides for prevention of vaginal transmission of HIV

Framework

Microbicides may be licensed based on results of only one effectiveness trial because:

- Urgent public health need – HIV epidemic is public health emergency
- Once effectiveness has been shown, conducting confirmatory placebo-controlled trials may be difficult for ethical reasons

However, does not leave much room for imperfection!

Licensing Based on Results of One Effectiveness Trial

Most drug regulatory agencies are likely to base their licensing assessment on:

- Appropriateness of trial design
- Level of effectiveness detected
- Generalizability of trial results
- Benefit-cost analysis based on 1-3 above, but also local incidence of HIV/STIs, and local predominant mode of HIV transmission and levels of condom use

Appropriate Trial Designs

- Trial should be appropriately designed and well-controlled, with a priori hypotheses and data analysis plans, and adequate randomization and blinding

See for example:

- ✓ *Mauck et al. for the International Working Group on Microbicides. Recommendations for the Clinical Development of Topical Microbicides - an Update. AIDS, 2001; 15(7): 857-868*
- ✓ *US FDA Guidance for Industry: Clinical Evidence of Effectiveness for Human Drug and Biologics Products, May 1998; <http://www.fda.gov/cder/guidance/1397fnl.pdf>*
- Trial should have multiple trial sites and investigators

Level of Effectiveness

Since likely to rely on one trial, that trial should have:

- Tight confidence intervals around overall effectiveness estimate
- Internal consistency across sub-groups, trial sites, and multiple endpoints

Challenges of Microbicide Effectiveness Trials

- HIV incidence always main primary endpoint; there are no validated surrogate endpoints
- HIV exposure at individual level generally not known; may only have estimate at population level
- Measure incremental effect over and above package of already proven HIV prevention interventions for ethical reasons
- Some microbicides may have lower method effectiveness than condoms
- Data on sexual practices, including microbicide and condom use, often unreliable
- As a result, most trials designed to detect modest effect sizes (30 and 50%)

Generalizability of Trial Results

When assessing the generalizability of trial results, drug regulatory agencies will most likely consider whether ...

- trial was multi-centered and/or multi-regional
- a wide range of sub-groups was included in the trial population, such as different age groups, and high and low frequency users

Alternatively, conduct bridging studies:

- May have to be focused on safety and acceptability
- May not be able to conduct studies in all countries and subgroups

Potential Public Health Impact

- Low effectiveness product may not be appropriate for registration in some settings, but very appropriate in others
- Mathematical modeling can be used to predict public health impact of a given product in certain settings – could aid regulators in their benefit-cost assessments

Other Regulatory Considerations Related to Effectiveness Trials

- **Over-the-counter versus prescription:**
 - Will depend on type of product, but ...
 - Microbicides should be available OTC as soon as possible to maximize public health impact
- **Product labeling:**
 - Avoid labeling for use with condoms only, but also avoid condom migration
 - Other challenges: potential partial effectiveness against HIV, full or partial effectiveness against STIs and pregnancy, and for some microbicides, potential for drug resistance

Licensing in Multiple Countries (1)

Barriers:

- Regulatory approval and licensing process varies widely among different countries in terms of approach, criteria, standards and requirements
- Some countries have limited resources to support regulatory infrastructure or scientific review, and may be heavily influenced by US Food and Drug Administration and European Medicines Evaluation Agency
- Some countries may require product registration in country of origin before they will consider approval in their country

Licensing in Multiple Countries (2)

- Rejection of an application by one country should not lead to automatic rejection by other countries – benefit-risk assessments for microbicides are likely to differ substantially in different parts of the world
- Concerns were raised that US regulatory policy may prevent microbicides from being registered, procured with US public funds, or exported to other countries if registration of such products is not approved by the US FDA

Recommendations for Next Steps

- Widely distribute meeting report to drug regulatory agencies, product sponsors, site investigators and other interested parties
- Clarify potential implications of US and other regulatory policy on microbicide registration, procurement and distribution; work towards removing barriers
- Encourage regional and global collaboration between drug regulatory agencies