

Regulatory Issues in Clinical Safety Studies

Report from WHO meeting

Scientific Basis for Regulatory Decisions on Microbicides

4-6 March 2002

Clinical Safety Group

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Remit

to identify core safety data with an emphasis on the regulatory perspective

Framework

Type of trial

Primary endpoint

safety (Phase I)

safety

expanded safety (Phase I/II)

safety

effectiveness (Phase II/III)

effectiveness

Regulatory structures

National authorities in place to implement legislation



Location(1)

in balancing risk and benefit, consider

- the likely countries of manufacture/development
- the epidemiology of the HIV pandemic

logistics (infrastructure)

clinical

laboratory

monitoring

Location(2)

Location

country of manufacture
(assume developed)

country of intended
effectiveness trial

both

Advantages

infrastructures in
place

safety & acceptability
informative;
early sensitisation of
authorities & community

avoids criticism of
exploitation

Disadvantages

acceptability data
of little relevance

may need to develop
infrastructure;
open to criticism of
exploitation

costly and potentially
time-consuming

Design

control

rationale for placebo (and/or observation) in early trials

- insufficient information on background rates of vaginal lesions in sexually active women

exposure

- aim to build up to 14 days of twice daily exposure
- development determined by pre-clinical toxicology and whether or not product is a new chemical entity

sample size

small (<10)

large (>20)

new entity

established entity

no absorption data

not absorbed

any concern about toxicity

safe in animals

Population

women

- sexually abstinent, HIV negative
- sexually active, HIV negative
- HIV infected, CD4 >200, clinically stable

men

- circumcised and non-circumcised, HIV negative

Either sexual exposure (ideal but difficult) or direct exposure

- HIV infected data desirable before effectiveness

Safety data on male partners during effectiveness also useful

adolescents

- important target group

Safety endpoints(1)

local

- role of colposcopy in clarification and documentation
- cervicovaginal lavage and biopsy considered research tools

systemic

- needed unless no absorption through breached genital mucosa

social

- events such as domestic violence considered related to microbicide use should be graded, recorded and reported

Safety endpoints(2)

Pap smear (cervical cytology)

- if abnormal, then exclude from safety and expanded safety
- aim to collect data prior to registration

Sexually transmitted and vaginal infections

- if present, then exclude from first safety trial
- during development, explore effect of concurrent medication

Consensus (1)

The aim of the study development plan is to collect sufficient safety data in: -

- sexually active women and their partners
- who are similar to the target population for effectiveness

as quickly as possible, in view of the urgent need and low level of concern regarding systemic toxicity for most of these agents

Consensus (2)

For the purposes of registration, need safety data that are: -

- representative of the general population
- including adolescents

Consensus (3)

Majority view: colposcopy

- should be routine in early safety trials
- is useful, but not necessary in expanded safety trials
- neither necessary nor practical in effectiveness trials

Minority view: colposcopy

- should be performed only if clinically indicated at all stages

Take home message

Think ahead to the instructions imparted by

- the health care worker giving the product out
- the woman herself when reading the information leaflet with over the counter product

They want to know how to use the product safely.

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