Clinical Development of Topical Microbicides

U.S. Regulatory Perspective

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Challenges

- **Clinical trials difficult to conduct**
- **Trials conducted primarily in non-US countries but sponsors intend to seek US regulatory approval**
- **Urgent need to establish the clinical effectiveness and safety of at least one candidate microbicide**

To Meet the Challenges

"Recommendations for the nonclinical development of topical microbicides for prevention of HIV transmission: An update", **JAIDS (in press)**

updated the 1996 recommendations

To Meet the Challenges

- In 2003, FDA sponsored an open Advisory Committee Meeting to discuss major trial design issues.
- Panelists: scientific experts, statisticians, consumer and industry representatives
- Outcome: some issues remain controversial; some good suggestions were provided by Committee.

Outline

- **Some trial design recommendations for the regulatory approval of first generation candidate microbicides**

  Phase 2/3 trial designs

  Controls (3-arm vs. 2-arm)

  Duration of follow-up

  Level of evidence (p-value)

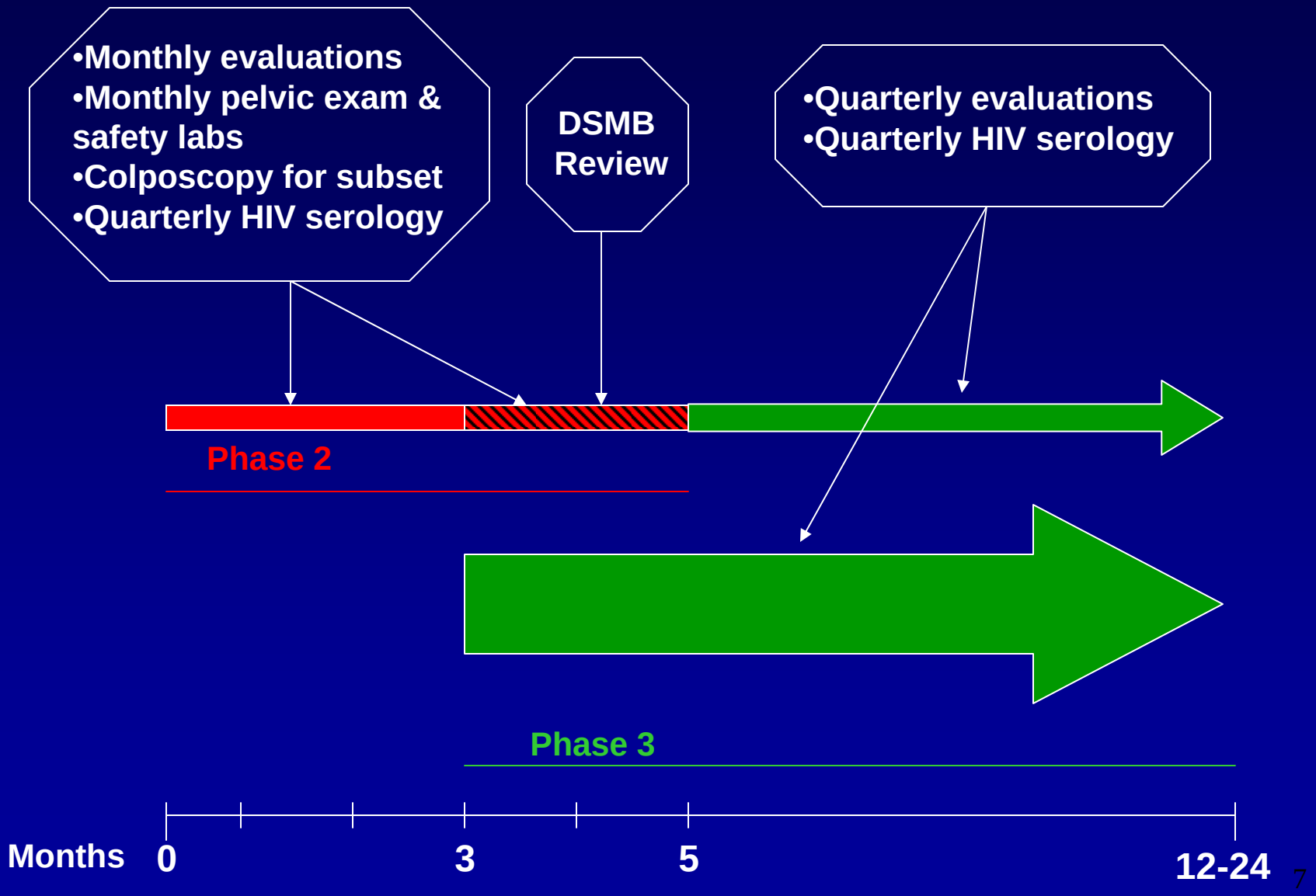
- **US bridging data**
- **Source documentation**
- **OTC development: help or hindrance?**
- **Regulatory tools for expediting development**

Phase 2 and 3 Trial Designs

- **Phase 2 run-in phase 3 with safety monitoring emphasized in phase 2**

Recommended by IWGM and Rockefeller Foundation Initiative

Phase 2 Run-In Phase 3 Trial



Phase 2 Run-in Phase 3

Critique

- **Design does not protect ineffective microbicide from going forward.**

Alternative Design

- **Intermediate size of the Phase 2/3 trial design as a screening trial (n=1/3 or ¼ of full size). If the product is plausibly effective, will be followed by 2 or 1 phase 3 trials.**

***Critique*:**

Introduces delay in development

Difficult to enroll subsequent ph. 3 trial(s)

How many trials do we need?

- Since 1962, effectiveness requirement:
  2 or more adequate, well controlled efficacy trials
- 1997 FDAMA codified: a single adequate and well controlled efficacy trial acceptable in some situations, e.g.

  Difficult to do second trial
  No other therapy

- Both acceptable: 2 trials or single trial

Two Trials

- **Independent execution; Parallel? Staggered?**
- **Support of conclusion of effectiveness:**

  Different designs ≥ Identical design

- **Level of evidence:**
  - **Trial 1** **p-value < 0.05 (two-sided)**
  - **Trial 2** **p-value < 0.05 (two-sided)**

Single Multi-center Trial

- No single site provides unusually large fraction of participants
- No single investigator or site provides a disproportionate favorable effect
- Consistency across study subset
- Statistically persuasive

Single Multi-Center Trial
Level of Evidence (p value, 2-sided)

- **P ≤ 0.001 : persuasive, robust**
  2*[0.025^2]=0.00125
- **0.05 > P ≥ 0.01: inadequate**
- **0.01> p > 0.001: acceptable, if:**

- good internal consistency

- low drop-out rates

- Other supportive data

Control Groups

- Placebo group (placebo + condom)
- Condom-only group

Do we need both?

Controls

- **The placebo group is necessary for blinding.**
- **The need for a ‘condom-only’ control group remains controversial.**
- **However, the inclusion of condom-only group adds critical information to the characterization of a placebo and important to the first generation of microbicide clinical trials, allowing 2-arm trials to be sufficient in subsequent trials.**

Length of Follow-up

- At least 12 months on-treatment follow-up
- Recommend study be continued until last subject completes 12 months.
- Off-treatment follow-up:
  - 1 month (if HIV incidence measured by viral load)
  - 3 months (if HIV incidence measured by seroconversion)

Acceptance of Non-US Data

- **Both acceptable:**

  - Under an Investigational New Drug Application (IND)

  ➢ **frequent scientific feedback**

  - not conducted under an IND

- **As sole basis for marketing approval:**
  'data are applicable to the U.S. population and U.S. medical practice'

U.S. Population

- **Primary goal: safety profile and acceptability; exposure duration comparable to non-US participants in microbicide trials**
- **A subset of U.S. participants in phase 2 run-in phase 3 trial, or**
- **U.S. data derived from contraceptive trials, or STIs prevention trials, e.g. chlamydia prevention in US women**

Documentation of Source Data

- FDA conducts field inspection to verify the validity of data.
- Source Data:

  Documents generated before the trial begins, during the conduct of the trial, and after completion or termination of the trial.

Source Documentation

to ensure data quality…..

…..Apply ALCOA principle…handwritten or e-recording..

- **Attributable: is it obvious who recorded it?**
- **Legible: can it be read?**
- **Contemporaneous: is the information in the correct time frame?**
- **Original: is it a copy; has it been altered?**
- **Accurate: are conflicting data recorded elsewhere?**

Ref: 21CFR 312.62 b and c, 21 CFR 312.68; ICH E6

OTC and Microbicide: Help or Hindrance?

- OTC use: ultimate goal
- Regulatory position differs internationally.
- In US, before microbicides can be made to public without prescription,
  - NDA and post-marketing data
  - Actual use study (n = many thousands)
  - Label comprehension study
  - Emergence of viral resistance data
- Prescription use makes product available to public sooner than direct OTC.

Regulatory Tools for Expediting Development

Fast Track Drug Development Program

- Pre-IND consultation, end-of-phase 1, 2-meetings, pre-NDA meeting
- Rolling submission of NDA
- Priority review (6 months, vs. standard 10 months)
- FDA usually seeks advice of outside expert scientific consultants or Advisory Committee for marketing approvability determination.

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&

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Definitions

Excerpts from GUIDANCE FOR INDUSTRY: Providing clinical evidence of effectiveness for human drug and biological products, May 1998.

- **Efficacy: 'refers to the findings in an adequate and well-controlled clinical trial or the intent of conducting such a trial'**
- **Effectiveness: 'refers to the regulatory determination that is made on the basis of clinical efficacy and other data.' 'Effectiveness of a new use may be extrapolated entirely from existing efficacy studies.'**

  Efficacy under clinical trial setting is the closest approximate of the effectiveness of the product under general population use.

Level of Evidence

P-value <

Number of Trials	One-sided $\alpha / 2$	Two-sided α	Level of Evidence
1	0.025	0.05	One Trial
2	0.025 each	0.05 each	Two Trials
2	0.025^2 =0.000625	0.00125	Two Trials
Single “LARGE”		0.001	Two Trials
Single “large”	0.025^1.5	0.008	One-and-half Trial

Replicating a Study Result

- **Probability of observing a statistically significant result (e.g. $p < 0.05$) upon repetition of a clinical trial when the effect size observed in the first trial is assumed to be the true effect**

Observed p-value	Probability of a significant result (Power) in future
0.05	50%
0.01	73%
0.001	91%

Reference: Goodman (1992), Statistics in Medicine, 875-879

Definition of a “Win”

HIV infection rate in

Microbicide < “Placebo” **p-value < 0.001 (two-sided)**

AND

Microbicide < Condom-only **p-value < 0.001 (two-sided)**

Overall $\alpha = 0.001$

Why win versus “Placebo” arm?

- **If the HIV infection rate in**
  - Microbicide ≈ “Placebo”
  - Microbicide < Condom
  - **then is “Placebo” as effective as Microbicide? (does not prove efficacy of microbicide)**

Why win versus Condom-only?

- **If the HIV infection rate in**
  - Microbicide + Condom < “Placebo” + Condom
  - Microbicide + Condom ≈ Condom
  - **then the use of microbicide in conjunction with condom does not provide any additional protection than condom alone**

Sample Size Estimates
(Duration of study=24 months, Power=90%)

Control Rate	Microbicide Rate	Effect Size	Sample Size (N)
6%	4%	33%	12,520
7%	4.67%	33%	10,797
9%	6%	33%	8,501
6%	3%	50%	4,993
7%	3.5%	50%	4,304
9%	4.5%	50%	3,385

Reference: Lachin,J. and M. Foulkes (Biometrics 1986)