



Scientific Advisory Board

Summary of Annual IPM SAB Executive Committee (EC) Meeting November 19-20, 2008

In opening remarks, Dr. Zeda Rosenberg, IPM CEO, described organizational changes at IPM in 2008 including recruitment for new senior leadership positions, renovation of the Clinical Trial Material (CTM) facility, and expansion of the headquarters and offices in South Africa. She reviewed IPM's responses to the recommendations of IPM's recently concluded 5-year donor-led evaluation, including increased engagement of the IPM SAB-EC and revised Phase III timeline projections.

Topics addressed during the two-day session included:

IPM Pipeline Management

Dr. Joseph Romano, Chief of Product Development at IPM, presented information on product pipeline prioritization at IPM. After applying a set of evaluation criteria to IPM's licensed active pharmaceutical ingredients (APIs), maraviroc, dapivirine, and tenofovir were designated the highest-priority compounds. Dapivirine ring, dapivirine gel, a combination dapivirine/maraviroc ring, a combination dapivirine/maraviroc film or gel, and a combination tenofovir/maraviroc film were identified as high-priority products. The SAB-EC concluded that IPM's product portfolio is well balanced and that the prioritization strategy employed is appropriate. Increased emphasis should be placed on backup products involving multiple mechanisms of action, so as not to rely solely on reverse transcriptase (RT)-inhibitor based microbicides. IPM should maintain parallel development programs for dapivirine ring and gel products, as well as accelerate the film program. It was agreed that IPM will need to continue to increase Research and Development (R&D) staff expertise and capacity to appropriately manage and advance its pipeline, and continue to outsource work as necessary.

Pipeline Prioritization in the Microbicide Field

Dr. Robin Shattock, Chair of the SAB-EC, led a discussion and review of relevant pipeline prioritization issues across the broader field of microbicides. There are three lead NNRTIs being developed in parallel (dapivirine, UC781, and MIV-150). The SAB-EC discussed the benefits and constraints to ensuring that only one compound from the NNRTI class be progressed to Phase III clinical evaluation as a single-agent product. It was noted that it is unlikely that all three drugs will be developed as single agents and/or will reach Phase III testing at the same time.

Regarding combination products, the SAB-EC recommended that IPM's development strategy follow the thesis that a combination product containing more than one drug may increase the breadth of protection against multiple viral clades/subtypes/strains of HIV. The potential increase in potency that a combination product may offer is a secondary benefit.

Tenofovir Development

IPM has coordinated a gap analysis (currently in draft stage) of the existing tenofovir (TFV) gel Investigational New Drug (IND) applications to determine the remaining studies that need to be conducted prior to initiation of Phase III or that would need to support a new drug submission should the results of CAPRISA 004 and/or VOICE studies show product efficacy. The implications of results from the currently ongoing Phase IIb CAPRISA study of 1.0% TFV gel on IPM's Phase III planning were discussed. If CAPRISA data are positive, IPM will need to revisit the current prioritization of its combination product pipeline. In 2009, IPM plans to initiate efforts to expand manufacturing capability for tenofovir gel.

Predictors of Safety and Efficacy

The issues of drug interactions and factors that could potentially enhance HIV infection with topical microbicides were discussed. It was agreed that the lowest effective local dose is ideal to minimize the systemic effects or pharmacological interactions of the microbicide. Since the minimum effective dose cannot be readily determined, IPM is basing dose selection on the highest-dose concentration achievable with low systemic exposure and no associated local or systemic toxicity. For IPM's product development, the SAB-EC agreed with the notion that pursuing multiple efforts, such as gene arrays and cytokine assays, as a means of predicting microbicide safety is not prudent since the interpretation of this type of data, given what is currently known in the field, would be ambiguous. The SAB-EC suggested the possibility that IPM investigate effects of products on target and inflammatory cells as a potential development tool. It was also recognized that true efficacy data cannot be collected in humans or in the laboratory before the Phase III trial, but informative pharmacodynamic (PD) data might be generated in Phase I/II clinical trials. The use of animal models to obtain PD data is another possibility that should be pursued.

PK/PD in Clinical Trials

IPM is moving forward with Pt-catalysed matrix vaginal rings, with a first pharmacokinetic (PK) study planned for 2009. Matrix rings have been prioritized over reservoir vaginal rings for dapivirine delivery, and currently there is no plan for additional clinical evaluation of dapivirine reservoir rings. The current lead dapivirine gel formulations, Gel 4759 and Gel 4789, which yielded similar initial clinical safety and PK findings, will continue to be tested

in upcoming clinical trials (expanded safety and PK/PD). The SAB-EC supports using an *ex vivo* PK/PD study design to obtain an efficacy indication for dapivirine prior to Phase III.

Also, PD could be investigated in the animal model as a supplementary tool, but not necessarily with the lead candidate and not necessarily by IPM. Such studies would constitute more basic model development and validation effort.

Resistance Analysis in Phase III Trial Design

The SAB-EC agreed that it is prudent for IPM to have a seroconverter protocol in place. IPM is planning intensive monitoring for seroconversion and will stop product administration if a positive HIV test result is obtained, unless test results are discordant. It is important that IPM attempt to isolate transmitted virus, and it was noted that single genome amplification might be used to achieve this. IPM reviewed the seroconverter protocols used by the Microbicide Trials Network (MTN) and those used in the HIV vaccine and PrEP trials for comparison. The fact that regulatory and ethics committees in Africa may require resistance testing to be performed locally, and that this is sometimes a condition of protocol approval, was discussed.

It was concluded that the incidence of drug resistance with the use of ARV-containing microbicides as well as the clinical and epidemiological consequences can only be sufficiently addressed in clinical trials. The SAB-EC agreed that comprehensive resistance and transmission studies should include long-term follow-up of women who have become infected while using microbicides. The IPM SAB-EC issued a consensus statement on resistance in October 2008. Please see http://www.ipm-microbicides.com/pdfs/english/ipm_publications/2008/FINAL%20IPM%20SAB%20EC%20Resistance%20Statement%20OCT%202008.pdf

HIV Testing Algorithm and End Point Monitoring

The SAB-EC agreed that use of a robust HIV testing algorithm in IPM's clinical trials is important. IPM is currently collaborating closely with several experts to establish its HIV testing algorithm; the MTN was identified as a valuable resource. HIV testing will be performed at the local level in IPM clinical trials. The issues and challenges associated with validation of HIV rapid testing in developing countries were discussed and are considered to be solvable. The SAB-EC inquired about standard-of-care and treatment options for trial participants with positive HIV test results during IPM clinical trials. It was explained that participants in IPM clinical trials will be tested frequently for HIV during the trial, and risk reduction counselling will be performed at every visit. If participants become infected with HIV during the trial, they will be referred for appropriate HIV-related care and ARV treatment. The threshold for initiation of ARV therapy will be determined with reference to the host country's treatment guidelines or, if those guidelines are not in place, through

guidelines established by the World Health Organization (WHO). IPM-supported research centres are typically established in areas where there is capacity for HIV-related care and administration of ARV treatment. For a full discussion of related issues, please see the document entitled “IPM Guidelines for the Conduct of Clinical Studies” http://www.ipm-microbicides.com/pdfs/english/ipm_publications/2008/FINAL_IPMEthicalGuidelines_%202nd%20Ed%20_%20Oct%2008_%20ENGLISH.pdf

Adherence

The advantages and disadvantages of IPM’s “smart applicator” as well as other types of adherence testing were discussed. The results of the pilot Daily Monitored Adherence (DMA) trials (IPM 014A and 014B) will show whether the DMA design is operationally feasible, but will not provide definitive data on its impact on adherence. It was observed that simply knowing that adherence was being monitored by the trial participants increased adherence rates in some clinical trials. In addition to measuring adherence to the trial protocol regarding product use, adherence to types of sexual activity (oral vs. vaginal vs. rectal) should also be monitored.

Communication Strategies for ARV-Based Microbicides

Information was presented on the various communication challenges that IPM and the microbicide field regularly face. The SAB-EC provided technical input on IPM’s capacity and approach with regard to communication advocacy, HIV prevention science literacy, and basic microbicide-related messages. The SAB-EC agreed that work in this area is a priority and that IPM’s fundamental strategy and approach is appropriate.

Restructuring IPM’s SAB Going Forward

Dr. Shattock described the proposed restructuring of the SAB, pursuant to a recommendation made during IPM’s 5-Year Evaluation. IPM is analysing various approaches and commissioned a review of how other product development partnerships have organized their SABs. Various options are under consideration, and a new SAB structure should be in place by the middle of 2009.

Summary Comments:

1. The SAB-EC favourably endorsed IPM’s pipeline prioritization strategy. Emphasis should be placed on backup products with alternative mechanisms of action so as not to rely solely on RT-inhibitor-based microbicides. Parallel development of the dapivirine ring and gel is appropriate. Development of vaginal films should be accelerated.
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2. The SAB-EC agreed that *ex vivo* PK/PD study assessments should be used to obtain surrogate efficacy indications prior to Phase III. Gene arrays and other cytokine expression assays are not recommended for inclusion in IPM's microbicide development approach. Some histology was suggested to investigate potential inflammatory effects of microbicide formulations.
3. Pt-catalysed dapivirine matrix vaginal rings and dapivirine gel formulations (Gel 4759 and Gel 4789) will be tested in upcoming clinical trials. Both dosage forms should continue to be developed in parallel towards initiation of Phase III evaluation.
4. It is prudent for IPM to have a seroconverter protocol in place. IPM needs to attempt to isolate transmitted virus and, if possible, use single genome amplification as a means of characterizing such viruses.
5. The SAB-EC agreed that promoting greater scientific literacy of HIV prevention and appropriate messaging to a variety of stakeholders and audiences is a priority and that IPM's fundamental strategy and approach is appropriate.

IPM SAB Executive Committee in attendance:

Richard Bax (ViroPharma Europe), Benjamin Cheng (PATH), David Friend (in lieu of Gustavo Doncel, CONRAD), Ian McGowan (in lieu of Sharon Hillier, University of Pittsburgh School of Medicine), Ruth Merkatz (Population Council), Thomas Moench (ReProtect), Lynn Paxton (CDC), Robin Shattock, Chair (St. George's University of London), Martin Springer (Merck, ret.), and Jens van Roey (Tibotec).
