



Scientific Advisory Board

Final Summary of SAB Executive Committee Meeting December 4, 2007

Opening remarks encompassed the introduction of the two new members of the Committee (Mr. Ben Chang, and Dr. Jens van Roey) and an overview of IPM's financial and staff resources. The stated purpose of the meeting was to review and address IPM's activities in four areas: Phase III product development, Phase III clinical, other pipeline development activity and market research.

Phase III Product Development

Detailed technical reviews of the dapivirine gel and IVR programs were presented, and these programs were strongly endorsed by the SAB. Overall, compared to one year ago when IPM had been devoting significant effort into expanding its microbicide compound portfolio, IPM R&D's primary focus has shifted to the product development efforts associated with its two Phase III candidates: dapivirine gel and ring. Significant effort has been devoted to solving manufacturing scale-up to support Phase III and commercialization. The SAB concurred that this was an appropriate shift in focus. The SAB recommended at times when IPM has to choose, because of human resource constraints, between long-term projects and the Phase III related development efforts, that IPM stay focused on progressing the current lead products for Phase III testing.

Specifically related to dapivirine development, dose selection was discussed and the SAB agreed it may be prudent for IPM to generate pharmacodynamic data for the dapivirine gel and ring to inform future efforts and help demonstrate proof of concept or failure.

Additionally, the issue of systemic levels of drug and the possibility for resistance generation was discussed. The SAB unanimously concurred that efficacy concerns currently outweigh resistance concerns in regard to making choices for product development. The SAB suggested addressing resistance issues to local Investigational Review Boards (IRBs) and National Ethics Committees in the form of a consensus statement, emphasizing that participants who seroconvert in clinical studies will be carefully monitored.

There was extensive discussion of the utility of the macaque model in microbicide product development. Limitations of the model were discussed, as well as its potential value. Some members of the SAB strongly recommended investigating the use of the model in some way. Others were far less enthusiastic about the relevance of the model. IPM agreed to proceed cautiously with considerations on the model.

Furthering their recommendation that IPM stay focused on a Phase III candidate, the SAB urged that IPM not wait for alternative delivery formulation options to be developed and to continue prioritizing the dapivirine gel and ring. Furthermore, if a significant time difference arises between the gel and ring, the SAB felt that IPM should not wait for the other one to catch-up.

Phase III Clinical

The SAB endorsed IPM's overall proposed Phase III trial design and cautiously supported the DMA (Directly Monitored Adherence) component (i.e. recommended pilot study and/or run-in) , expressing that the microbicide field as a whole will learn and benefit from IPM undertaking this study. In addition, the SAB cautioned IPM to be cognizant of the fact that daily interactions with study participants while conducting clinical trials could have an effect on the study outcome. Since adherence monitoring is important for both gels and rings, the SAB suggested IPM consider an adherence "run-in" to a Phase III trial. Additional specific recommendations/ considerations included: (1) recognition that a DMA approach could have differential effects on incidence if populations using an IVR versus a gel; (2) IPM consider the use of processes for compliance screening prior to enrollment (e.g., allow for two weeks+ of product use, followed by assessment of plasma levels. If product use is not confirmed, the participant is screened out of the program.).

Early-Stage Pipeline Development Activity

IPM pipeline products, including a CCR5 inhibitor, DS001, licensed from Merck & Co., Inc. and a gp120 inhibitor, DS003, licensed from Bristol Myers Squibb were discussed. The SAB recognized that IPM has made significant progress in creating a pipeline with multiple mechanisms of action and still supports acquisition of additional compounds if they are late in development and/or have a significant clinical package.

Market Research

Finally, IPM's current and planned market research studies were outlined. The SAB emphasized that acceptability data for a film formulation is important to generate, and encouraged IPM to continue their market research efforts, and endorsed the overall value of this research to the microbicide field.

In conclusion, the SAB congratulated IPM for their progress and for providing a comprehensive update of the past year's efforts.

Note: Prior to the SAB Executive Committee meeting, all members received a comprehensive written update on all of the internal and external programs at IPM.

Summary Comments:

1. The SAB favorably endorsed the IPM scientific program encompassing pipeline expansion, product development, microbicide related research, clinical evaluation, and market research efforts, in terms of progress made and plans going forward.
2. The SAB strongly recommended a more focused, prioritized approach, given limitations at the staffing level, as well as the expansion of capacity at the staff level.
3. Although favorably reviewed, the SAB constructively made specific recommendations and noted specific concerns regarding the phase III trial design approach.