Mid-term Performance Report, Year 1

Advancing the Microbicide Pipeline

30 September 2013 – 31 March 2014

Cooperative Agreement No. AID-OAA-A-13-00096

Office of HIV/AIDS

Submitted 30 April 2014

International Partnership for Microbicides
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CONTENTS

A. EXECUTIVE SUMMARY .................................................................................................................................................. 1

B. ACTIVITY SUMMARY: MID-TERM PROGRESS AND PLANS GOING FORWARD .................................................. 2
   Activity 1: DS003-based Tablet .................................................................................................................................... 2
   Activity 2: Combination-ARV Rings ............................................................................................................................. 4
   Activity 3: Investigation of New ARV Compounds for Development ........................................................................... 6

C. GENDER .......................................................................................................................................................................... 6

D. HUMAN SUBJECTS PROTECTION ................................................................................................................................. 7

E. ENVIRONMENTAL COMPLIANCE ................................................................................................................................. 8

F. SUCCESS STORIES ............................................................................................................................................................ 8

G. PRESS & MEDIA ............................................................................................................................................................... 8

H. BEST PRACTICES .............................................................................................................................................................. 9
A. EXECUTIVE SUMMARY

IPM’s product development program aims to progress a diverse portfolio of microbicide products based on a range of promising antiretroviral (ARV) drugs and dosage forms through preclinical and early-/mid-stage clinical testing. The need to continue advancing the microbicide pipeline is twofold: (1) multiple product options need to be developed to enable women to choose which one(s) best fit their needs and preferences; and (2) the HIV prevention field cannot afford to wait until drug resistance occurs to begin developing additional HIV prevention drugs. While promising candidates are currently in Phase III testing, IPM will continue advancing highly potent ARV drugs, including those not currently used for HIV treatment and those that can be combined with other ARVs, through the pipeline. As such, this Cooperative Agreement comprises the following activities: (1) advancing a candidate based on DS003 (a gp120-binding entry inhibitor not currently used in HIV prevention or treatment) through early clinical trials; (2) advancing a combination-ARV vaginal ring through formulation and preclinical development; and (3) identifying and evaluating new and early development ARV compounds with alternative mechanisms of action for pipeline progression.

**Progress and Achievements: Year 1 Mid-Term**

In the first six months of this award (30 September 2013 – 31 March 2014), IPM has:

- Synthesized 2 batches of DS003 drug substance under Good Manufacturing Practice (GMP) (non-USAID funding)
- Defined the formulation and initiated stability assessments of a single-use DS003 vaginal tablet developed at the University of South Australia (non-USAID funding)
- Conducted competitive bidding processes to identify: (1) GMP manufacturer for DS003 tablet; and (2) a partner for DS003-based vaginal ring development
- Completed *in vitro* pharmacokinetic (PK) assessments of DS003 (non-USAID funding) and prepared to conduct key DS003 preclinical toxicology studies
- Conducted a pre-IND (Investigational New Drug) consultation with the FDA for DS003 development; IPM’s product development plans to advance a DS003 tablet to Phase I evaluation were supported
- Initiated re-testing of maraviroc plasma samples from the Phase I maraviroc-based ring trial (MTN-013/IPM 026) to inform product development plans for maraviroc
- Continued discussions with pharmaceutical company partners regarding access to new ARV compounds

### Advancing the Microbicide Pipeline: Workplan Timeline, Year 1

<table>
<thead>
<tr>
<th>Activity 1: DS003-based Tablet</th>
<th>2013</th>
<th>2014</th>
<th>MID-TERM STATUS OVERVIEW</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUB-ACTIVITY 1: Formulation, Manufacturing, Analytical Development</td>
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<tr>
<td>Contract Manufacturing Organization (CMO) evaluation and selection</td>
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<td>Technology transfer to CMO</td>
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<td>Non-GMP production</td>
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<td>Analytical method development/validation</td>
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<tr>
<td>Initiation of stability testing</td>
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<td>SUB-ACTIVITY 2: Preclinical Development</td>
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<tr>
<td>Rabbit vaginal irritation study</td>
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<tr>
<td>Reproductive toxicity studies</td>
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<tr>
<td>SUB-ACTIVITY 3: Regulatory and Other Exploratory Efforts</td>
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<tr>
<td>Pre-IND consultation with FDA</td>
<td></td>
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<tr>
<td>Efforts to access additional entry inhibitor compounds</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Activity 2: Combination-ARV Rings</th>
<th>2013</th>
<th>2014</th>
<th>MID-TERM STATUS OVERVIEW</th>
</tr>
</thead>
<tbody>
<tr>
<td>Re-analysis of MTN-013/IPM 026 clinical samples (new activity)</td>
<td></td>
<td></td>
<td>Ongoing</td>
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<tr>
<td>Vendor identification and contracting</td>
<td></td>
<td></td>
<td>Ongoing</td>
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<tr>
<td>Active Pharmaceutical Ingredient (API) interaction studies</td>
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<td></td>
<td>Planned for Q2 2014</td>
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<tr>
<td>API combination + polymer system interaction studies</td>
<td></td>
<td></td>
<td>Planned for Q2 2014</td>
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<tr>
<td>Analytical method adaptation/validation</td>
<td></td>
<td></td>
<td>Planned for Q2 2014</td>
</tr>
<tr>
<td>Development of prototype rings</td>
<td></td>
<td></td>
<td>Planned for Q2 2014</td>
</tr>
<tr>
<td>Initiation of non-GMP stability assessment</td>
<td></td>
<td></td>
<td>Planned for Q2 2014</td>
</tr>
<tr>
<td>Initiation of preclinical evaluations</td>
<td></td>
<td></td>
<td>Planned for Q2 2014</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Activity 3: Investigation of New ARV Compounds for Development</th>
<th>2013</th>
<th>2014</th>
<th>MID-TERM STATUS OVERVIEW</th>
</tr>
</thead>
<tbody>
<tr>
<td>Field survey and discussions ongoing</td>
<td></td>
<td></td>
<td>Ongoing</td>
</tr>
</tbody>
</table>
Obstacles and Challenges: Year 1 Mid-Term

PK data from the MTN-013/IPM 026 trial prompted additional analyses of the clinical samples which IPM felt was important to conduct before continuing development work on maraviroc-based rings, as initially described in the Year 1 Workplan. USAID approved re-directing of funds for this purpose and these analyses are currently ongoing. IPM is also supporting the implementation of a Phase I rectal and vaginal maraviroc gel trial (to be conducted under the NIH/NIAID funded CHARM U19 grant to the University of Pittsburgh) which will offer key data on vaginal use of maraviroc which will inform future development efforts. The trial is targeted for initiation in Q4 2014 (non-USAID funding).

IPM is working to understand and adhere to the USAID procurement guidelines and process required for making sub-awards to contractors. IPM is now allowing for additional time needed to complete the elements of the procurement package and USAID approval process to minimize any delays in implementing project activities.

B. ACTIVITY SUMMARY: MID-TERM PROGRESS AND PLANS GOING FORWARD

This section describes progress made in meeting Year 1 objectives during the performance period (30 September 2013 – 31 March 2014), with an overview of planned activities for the next performance period (01 April – 29 September 2014).

Activity 1: DS003-based Tablet

Primary Countries of Activity: United States, TBD in Europe

Technical Coordinator: Bríd Devlin, Exec. Vice President, Product Development

Implementers: IPM; contractors TBD

Objective: The primary objective of this activity is to determine the safety, tolerability and acceptability of DS003 administered vaginally to healthy, HIV-negative women by advancing a DS003-based tablet through first-in-human Phase I clinical evaluation. A single-use tablet will allow for a small, stepwise dose-escalation evaluation which will support and inform other DS003-based formulation efforts such as a vaginal ring. In parallel with the preclinical development of DS003, IPM will attempt to gain access to and evaluate other promising gp120 entry inhibitor compounds currently in development.

Activity Description: DS003 is a small molecule compound originally developed by Bristol Myers-Squibb (BMS) licensed to IPM in 2005, with worldwide rights, for development as a microbicide product. This class of compounds (gp120-binding entry inhibitors) has been shown to have potent inhibitory effects on HIV-1. DS003 is an important microbicide candidate for several reasons: (1) it acts early in the HIV lifecycle, potentially increasing the chances of protection; (2) the target is the virus itself rather than the host cell, reducing the likelihood of unwanted secondary effects; (3) this mechanism of action is not in use for HIV treatment or prevention, which means that (a) if resistance to DS003 were to occur in an infected individual unaware of their status and using a DS003-based microbicide, it is unlikely to compromise current treatment options, and (b) the increasing use of ARVs for treatment of HIV/AIDS in developing countries is unlikely to result in HIV strains that are resistant to DS003; and (4) as a small molecule ARV, DS003 can be developed as a microbicide, either alone or combined with other ARVs. It is anticipated that the DS003-alone tablet formulation will be the subject of the initial DS003 IND filing and first-in-human clinical trial, which would be conducted via partnership with an existing clinical network, such as the NIH-funded Microbicide Trials Network (MTN). Future development of DS003 will likely be in combination with other ARVs given the advantages of combining two APIs, and the fact that DS003 is not active against subtype AE viruses.

Sub-Activity 1: Formulation, Manufacturing and Analytical Development. Implementation of the current tablet production process at a GMP manufacturer will be necessary to provide materials for the proposed Phase I clinical trial. Analytical testing to support formulation, process implementation and drug product stability will also be performed, as well as clinical packaging and labeling work necessary for the Phase I trial.

Sub-Activity 2: Preclinical Development. Several preclinical and toxicology studies are planned and underway, including a set of reproductive toxicology (Segment I and II) studies and a 14-day vaginal irritation study in rabbits with the vaginal tablet formulation. IPM is also pursuing parallel limited development of DS003 ring, film and gel formulations for evaluation in a macaque PK and efficacy study comparing DS003 dosage forms, targeted for 2014.

Sub-Activity 3: Regulatory and Other Exploratory Efforts. In Q1 2014, IPM submitted a pre-IND request and questions which covered the toxicity program as well as the preliminary Phase I trial design, to support the first-in-human
DS003 tablet trial. Written responses were provided by the FDA supporting IPM’s continued development of the DS003 tablet for clinical evaluation. Also as part of this program, IPM will explore the possibility of performing a comparative analysis between DS003; the small-molecule inhibitor BMS-626529; BMS-663068 (a prodrug for BMS-626529 with the same mechanism of action as DS003, currently in Phase II clinical testing for HIV treatment); and any other promising gp120 inhibitor compounds available from BMS.

**Progress in Past 6 Months:** During the performance period (30 September 2013 – 31 March 2014), IPM made progress toward the Year 1 expected results for this activity, as shown in the timeline below.

### Activity 1: DS003 Tablet
**Year 1 Workplan Expected Results**

<table>
<thead>
<tr>
<th>Activity</th>
<th>2013</th>
<th>2014</th>
<th>Status at 31 March 2014 (Major Milestones)</th>
<th>Plans for Next Performance Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMO evaluation and selection</td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Technology transfer to CMO</td>
<td></td>
<td></td>
<td>Delayed to Q2 2014</td>
<td>Technology transfer pending CMO contract</td>
</tr>
<tr>
<td>Non-GMP production</td>
<td></td>
<td></td>
<td>Delayed to Q3 2014</td>
<td></td>
</tr>
<tr>
<td>Analytical method development/validation</td>
<td></td>
<td></td>
<td>Delayed to Q2 2014</td>
<td></td>
</tr>
<tr>
<td>Initiation of stability testing</td>
<td></td>
<td></td>
<td>On track for initiation in Q3 2014</td>
<td></td>
</tr>
<tr>
<td>SUB-ACTIVITY 2: Preclinical Development</td>
<td></td>
<td></td>
<td>Study protocol outlined</td>
<td>Initiation delayed to Q3 2014</td>
</tr>
<tr>
<td>Rabbit vaginal irritation study</td>
<td></td>
<td>✓</td>
<td>Study protocol outlined; vendor selected</td>
<td>On track for study initiation in Q3 2014</td>
</tr>
<tr>
<td>Reproductive toxicity studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SUB-ACTIVITY 3: Regulatory and Other Exploratory Efforts</td>
<td></td>
<td></td>
<td>Achieved: Q1 2014 (<strong>pre-IND package to FDA Jan-14; written responses received Feb-14 supporting IPM’s DS003 product dev. plans</strong>)</td>
<td></td>
</tr>
<tr>
<td>Pre-IND consultation with FDA</td>
<td></td>
<td>✓</td>
<td></td>
<td>Ongoing</td>
</tr>
<tr>
<td>Efforts to access additional entry inhibitor compounds</td>
<td></td>
<td></td>
<td></td>
<td>Additional discussions scheduled for Q2 2014</td>
</tr>
</tbody>
</table>

**Planned Activities for Next 6 Months:** IPM will continue to execute the Year 1 Workplan during the next performance period (01 April 2014 – 29 September 2014). Specifically, IPM will continue working toward achieving the following results expected by completion of Year 1:

- Engagement of CMO for GMP manufacture of DS003 vaginal tablets, completion of technology transfer activities and initiation of non-GMP tablet production
- Initiation of 14-day rabbit vaginal irritation study with DS003 tablet
- Initiation of Segment I (rats) and Segment II (rats and rabbits) reproductive toxicity assessments
- Initiation of a macaque PK study comparing DS003 dosage forms (non-USAID funding)
- Continuation of discussions with BMS regarding access to alternative entry inhibitor compounds
Activity 2: Combination-ARV Rings

Primary Countries of Activity: United States, TBD in Europe  
Period: 2006–2018

Technical Coordinator: Brid Devlin, Exec. Vice President, Product Development  
Implementers: IPM; contractors TBD

Objective: The main objective of this activity is to advance combination microbicide vaginal rings containing dapivirine, maraviroc and DS003 through formulation and preclinical development. Dapivirine is a non-nucleoside reverse transcriptase inhibitor (NNRTI), and maraviroc and DS003 are both viral entry inhibitors although they act on different targets (host cell CCR5 co-receptor and viral gp120, respectively). A multi-ARV microbicide ring product is a priority for IPM and the wider microbicide field because (1) the use of multiple APIs with varying mechanisms of action is likely to provide greater (possibly synergistic) inhibitory activity against HIV; and (2) a microbicide containing a combination of ARVs is likely to maintain efficacy even if an individual is exposed to viral strains with mutations conferring resistance to one of the active ingredients, because the other ARV will act as a ‘safety net.’ Thus, there is a strong scientific rationale for exploring combinations of dapivirine, maraviroc and DS003 in a microbicide product, and a ring dosage form is being pursued due to the reduced burden of compliance with this type of product.

Activity Description: In the development of a multi-ARV product, it is important to assess the potential efficacy and risks around the individual components. IPM has already done varying degrees of development on vaginal microbicide rings containing dapivirine alone; dapivirine and DS003; maraviroc alone; and dapivirine and maraviroc (summarized below). All of this past work will serve as a platform upon which to develop a combination-ARV ring for clinical evaluation.

Dapivirine: IPM has developed a silicone-based vaginal ring delivering dapivirine over 28 days that is currently being assessed in two parallel Phase III trials (IPM 027 and MTN-020), and thus there is substantial preclinical and clinical data to support the incorporation of dapivirine in a new ring. IPM has also worked with partner Particle Sciences, Inc. (PSI) to develop prototype rings combining dapivirine and DS003 in an ethyl vinyl acetate (EVA)-based polymer.

Maraviroc: This CCR5 antagonist was licensed to IPM in 2008 from Pfizer (now ViiV Healthcare) and has a large volume of safety and efficacy data available from currently marketed HIV treatments (Selzentry/Celsentri®). In addition, information from an initial Phase I study of a dapivirine-maraviroc vaginal ring (MTN-013/IPM 026) provides key PK and pharmacodynamic (PD) data to inform the design of future maraviroc-based rings.

DS003: As described in Activity 1 above, IPM is progressing a DS003-only vaginal tablet program in order to collect necessary preclinical information on DS003, with the goal of assessing its safety and tolerability when administered vaginally to women in a Phase I study. As such, it is anticipated that there will be sufficient safety information available for DS003 in advance of any regulatory submissions or clinical study initiation with a combination ring containing this compound.

In 2013, data emerged from the MTN-013/IPM 026 clinical trial of maraviroc based rings. The method used originally for the analysis of maraviroc in plasma samples from the trial had a lower limit of quantification (LLOQ) of 0.5 ng/mL, and no maraviroc was detected in any of the trial samples. IPM felt there would be value in reanalyzing these samples using a more sensitive assay, and requested USAID support under this Activity for this purpose. This data will be key to informing further development efforts with maraviroc.

Initial activities for this program will focus on formulation and defining the Target Product Profile (TPP) and lead ring design. Preliminary work has shown that all three agents are compatible with the polymer EVA and this will be used as a starting point for formulation design. If needed, other thermoplastic polymers, such as polyurethane, will be explored.

The regulatory and clinical development strategies for microbicides containing more than one API are unclear at present. One of the key challenges is the regulatory expectation that the benefit of the combination over the individual drugs is demonstrated, which will likely necessitate the parallel development of rings containing each single agent as a part of this program. IPM will maintain ongoing dialogue with regulatory authorities to clarify the optimum pathway forward for a combination product.

Progress in Past 6 Months: During the performance period (30 September 2013 – 31 March 2014), IPM made progress toward the Year 1 expected results for this activity, as shown in the timeline below.
**Activity 2: Combination-ARV Rings**

<table>
<thead>
<tr>
<th>Year 1 Workplan Expected Results</th>
<th>2013 Q4</th>
<th>2014 Q1</th>
<th>2014 Q2</th>
<th>2014 Q3</th>
<th>Status as of 31 March 2014 (Major Milestones)</th>
<th>Plans for Next Performance Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Re-analysis of MTN-013/IPM 026 clinical samples</td>
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<td></td>
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<td>Ongoing at Tandem Labs</td>
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<tr>
<td>(new milestone)</td>
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<tr>
<td>Vendor identification and contracting</td>
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<td></td>
<td>✓</td>
<td></td>
<td><strong>Achieved: Q1 2014</strong> <em>(DS003-based ring development</em>&lt;br&gt;**(partner selected: Queens University Belfast, UK)*</td>
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<tr>
<td>API interaction studies</td>
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<td></td>
<td>Delayed to Q2 2014 following completion of&lt;br&gt;contracting process</td>
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<tr>
<td>API combination + polymer system interaction studies</td>
<td></td>
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<td></td>
<td>Delayed to Q2 2014</td>
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<tr>
<td>Analytical method adaptation/validation</td>
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<td>Delayed to Q2 2014</td>
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<tr>
<td>Development of prototype rings</td>
<td></td>
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<td></td>
<td>Delayed to Q3 2014</td>
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<tr>
<td>Initiation of non-GMP stability assessment</td>
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<td>Delayed to Q4 2014</td>
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<tr>
<td>Initiation of preclinical evaluations</td>
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<td></td>
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<td></td>
<td>Delayed to Q4 2014</td>
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</table>

The re-analysis of clinical samples from MTN-013/IPM026 was a new activity approved by USAID under the Year 1 Workplan. IPM has access to a more sensitive assay (LLOQ = 6 pg/mL) which has been used to re-analyze samples from Days 1 and 28; this detected low, but measurable, concentrations in samples from Day 1, but not samples from Day 28.

IPM has requested that MTN provide data from the analysis of maraviroc in vaginal fluid samples from the trial, to examine how drug release from the ring changes over the 28-day use period. Based on this assessment, further re-analysis of plasma samples from other time points may be performed.

**Planned Activities for Next 6 Months:** IPM will continue to execute the Year 1 workplan during the next performance period (01 April 2014 – 29 September 2014). Specifically, IPM will continue working toward achieving the following results expected by completion of Year 1:

- Additional re-analysis from the Phase I MTN-013/IPM 206 maraviroc-based ring trial may be performed at expanded time points
- Engagement of partner for development of DS003-based rings, production of prototype rings and initiation of stability and preclinical testing
- Continued support of the planned CHARM-03 trial of maraviroc gel, used rectally and vaginally (non-USAID funding)
Activity 3: Investigation of New ARV Compounds for Development

Primary Countries of Activity: United States, TBD in Europe

Technical Coordinator: Brid Devlin, Exec. Vice President, Product Development

Objective: The main objective of this activity is to identify and evaluate new and promising microbicide candidates with alternative mechanisms of action for development by working in collaboration with global partners.

Activity Description: IPM will continue to survey the field and consult with partners and pharmaceutical companies to identify new and promising ARV compounds for microbicide development. Of particular interest are compounds that target the HIV protease and integrase enzymes which have not previously been tested as microbicides in humans and may have important benefits for HIV prevention, as well as alternative entry inhibitors.

**Darunavir:** This compound works by blocking the HIV enzyme protease, which prevents the host cell from producing new viruses. As a marketed product for HIV treatment (PREZISTA®), it has robust preclinical and clinical packages of data available which will streamline the microbicidal development pathway. Additionally, IPM has successfully partnered with Janssen R&D Ireland (formerly Tibotec) on its dapivirine program since 2004, providing a strong relationship and a solid starting point for license agreement negotiations.

**GSK1265744:** ViiV Healthcare’s promising candidate acts by blocking the HIV enzyme integrase, preventing the viral DNA from being integrated into the host cell genome. It is currently in development as a long-acting injectable, both for HIV treatment and prevention, and is also being considered for development as a vaginal microbicide. This compound represents a promising integrase inhibitor to add to the microbicidal pipeline given its novel mechanism of action (from a prevention perspective) and its potential as a long-acting product because of its demonstrated PK properties. IPM also has a strong partnership with ViiV Healthcare, as the provider of IPM’s maraviroc license (since it was transferred from Pfizer in 2010).

If IPM is successful in securing access to these compounds, they will be evaluated for formulation and cost feasibility, and early safety and anti-HIV activity assessments will be performed. If promising, IPM will attempt to negotiate license agreements that support IPM’s charitable mission, and these promising candidate(s) will be progressed through an evidence-based early development program toward a defined TPP. This will include early formulation and analytical development activities as well as preclinical studies, and establishing a formal cross-functional Product Development Team, TPP and Development Plan.

Progress in Past 6 Months: During the performance period (30 September 2013 – 31 March 2014), IPM made progress toward the Year 1 expected results for this activity, as shown in the timeline below.

<table>
<thead>
<tr>
<th>Activity 3: New ARV Compounds</th>
<th>2013</th>
<th>2014</th>
<th>Status as of 31 March 2014 (Major Milestones)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 1 Workplan Expected Results</td>
<td>Q4</td>
<td>Q1</td>
<td>Q2</td>
</tr>
<tr>
<td>Field survey and discussions ongoing</td>
<td></td>
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</tbody>
</table>

IPM also continued to collaborate with the EC-funded CHAARM Consortium on development of a dapivirine-darunavir microbicide. A Phase I trial of the combination gel is targeted to initiate in 2014 (non-USAID funding)

Planned Activities for Next 6 Months: IPM will continue to execute the Year 1 workplan during the next performance period (01 April 2014 – 29 September 2014). Specifically, IPM will continue working toward achieving the following results expected by completion of Year 1:

- Continuing dialogue with ViiV Healthcare regarding access to GSK1265744
- Continuing to support development of a dapivirine-darunavir microbicide with EC CHAARM Consortium and continued dialogue with Janssen R&D Ireland regarding access to darunavir

C. **GENDER**

IPM is working to develop female-initiated HIV prevention products specifically because of the disproportionate impact this virus has on women in the developing world, particularly in sub-Saharan Africa. All of IPM’s work stems from the recognition that there are currently no tools women can use to discreetly protect themselves from HIV infection, and the social context within which many African women live constricts their ability to use the most effective HIV prevention
methods without the active participation of a male partner (i.e., abstinence, condom use, mutual monogamy, male circumcision). It is hoped that the monthly dapivirine vaginal ring meets women’s expressed interest in a convenient HIV prevention method that would not require negotiation with a male partner.

IPM is committed not only to understanding the influence of gender roles on project objectives, but also to the ultimate goal of promoting gender equality. To this end, the organization recognizes that gender considerations must be integrated into the product development pathway for microbicides. Consistent with USAID expectations, IPM utilizes gender analyses to guide development activities as well as long-term planning. Each of the areas described below demonstrates a specific example of IPM’s dedication to ensuring gender equality through integrating and understanding of the impact of gender issues on organizational goals.

**Clinical Programs:** To better understand how to mitigate potential barriers to microbicide use, IPM collects social and behavioral data from women enrolled in its trials as well as a subset of participants’ male partners. These data focus on trial-related product use as well as the broader social, cultural and gender norms that might influence sexual behavior. Male partner interviews focus on gender roles and norms that may facilitate or impede adherence to product use in current and future IPM trials, and foreshadow male partner influence on microbicide uptake and correct, consistent and continued use. For example, in IPM 011, a safety and acceptability study of a placebo vaginal ring in several sub-Saharan African countries, data was gathered from some study participants with regard to using a vaginal ring to prevent HIV infection without disclosing use to their partners. Data indicated that although women may value having the choice of disclosing ring use to their partner, whether they can actually exercise that choice will depend on specific aspects of their relationship as well as social and cultural norms. Although 65% of trial participants said they would use the ring without telling their partner, 63% said their partner might become angry if he was not told, and 13% of these respondents further indicated that their partner might become violent. These social and behavioral data serve the secondary clinical trial objectives of assessing acceptability and adherence, as well as the goal of developing a database to inform future microbicide research and introduction efforts.

**Assessment of Gender-Based Violence:** It is inconclusive whether or how the availability of vaginal microbicides might exacerbate the problem of gender-based violence, given that some men may oppose their use. IPM recognizes that its local partners may need to address this issue as part of the larger women’s health and empowerment movement salient to their communities. Thus far, there has been no general social movement against microbicide trial participants. To the contrary, community support for HIV prevention efforts in general, and for microbicides in particular, remains strong. IPM trials routinely monitor and collect data on social harms, which include physical, emotional and financial harms experienced by participants during the trial. Collaborating research centers have strategies and referral resources in place to mitigate the effects of such harms, and there have been no significant findings to suggest that an increased incidence of social harms to study participants have occurred as a result of their participation in IPM clinical trials.

**Community Relationships:** Where IPM conducts its clinical trials, the RCs have established Community Advisory Groups (CAGs), which routinely include representation from groups working on gender issues. This has become common practice for HIV prevention research and facilitates inclusive community participation. The most notable risk of exacerbating inequalities is partnering with community groups that, inadvertently or otherwise, maintain an inequitable status quo. IPM will continue to engage with communities for microbicide introduction efforts, and it will be necessary to extend to groups outside of the clinical research setting. At this point, another round of assessments will be needed to systematically identify additional effective and appropriate community groups with which to partner.

**D. HUMAN SUBJECTS PROTECTION**

IPM holds a Federal Wide Assurance, which attests to IPM’s intent and ability to conduct Human Subjects Research according to guidelines required by the US Government. IPM’s FWA number is FWA00018657 and is currently valid through 13 March 2019. IPM conducts research in full compliance with internationally recognized guidelines for GMP, Good Clinical Practice (GCP) and Good Clinical Laboratory Practice (GCLP), in accordance with the Council for International Organizations of Medical Sciences (CIOMS). For all IPM clinical trials, participants are asked to sign an informed consent form in advance of any study procedure. Informed consent information sheets/forms are approved by the institutional review boards/independent ethics committees and regulatory authorities responsible for approving research conducted at each research location.
E. ENVIRONMENTAL COMPLIANCE

The investigational vaginal products for the proposed activities will be prepared for research and clinical trial purposes only. The manufacturing steps involved in the preparation of the clinical material will be carried out in accordance with applicable environmental regulations, including disposal or destruction of waste materials. Vaginal products used by participants in clinical trials during development are either collected for potential post-use evaluation, or disposed of as biohazard clinical waste per study protocol. In this regard, the activities conducted as part of this award are consistent with the exclusions described in Federal Regulations 22 CFR 216.2(c)(2), and will not require an Initial Environmental Examination, Environmental Assessment and Environmental Impact Statement.

F. SUCCESS STORIES

IPM expects that Phase I readiness of one or more new microbicide candidates will be the greatest success generated by the activities implemented under this Cooperative Agreement. However, as this report reflects the first six months of this new award, IPM does not have documented success stories to share as of yet. Organizational successes achieved during calendar year 2013 will be described in IPM’s Annual Report, which will become available in Q3 2014.

G. PRESS & MEDIA

Descriptions of all media coverage that appeared during the performance period (30 September 2013 – 31 March 2014) are provided below; clippings and additional information is included in this report as an appendix.

Summary of IPM Public Statements and Messages

IPM Receives 2 Awards from USAID Through PEPFAR to Advance HIV Prevention Technologies for Women (21 Oct 2013)

- Picked up by UNAIDS Daily News Clips (24 October 2013) and PEPFAR Daily News Clips (14 November 2013)

The Promise of Progress in 2014 (1 January 2014)

IPM Announces Dr. James McIntyre as Board Chair, New Board Members Ms. Heidemarie Wieczorek-Zeul and Mr. Michael Stevens (24 January 2014)

Two Studies Advance HIV Prevention Options for Women (4 March 2014)

- Cross posted on Armenian Medical Network, eWallstreeter, Infection Control Today, Science Codex, Science Newsline, allAfrica and News Medical

International Women's Day: Inspiring Ideas for Women's Health (8 March 2014)

Congressional Briefing, 22 October 2013

Dr. Zeda Rosenberg participated in the Congressional briefing, “Saving lives through research: USAID’s role in creating breakthrough global health products,” hosted by Global Health Technologies Coalition (GHTC) and PATH. The event aimed to encourage continued investment in research for and development of new and innovative global health products, and the media coverage reflected this overarching objective.

Print/Digital Media

- GHTC Breakthroughs Blog: No more business as usual: USAID’s important role in global health R&D highlighted at Capitol Hill briefing
- Science Speaks Blog: Supporting Global Health Technologies Act, speakers warn: time is running out on tools for infectious diseases

Social Media

- IPM live-tweeted during the briefing; GHTC and PATH retweeted IPM throughout the event

New USAID Grants (4 November 2013)

A piece on the Science Speaks Blog highlighted IPM’s recent grants from USAID and discussed how they have helped to generate new, critical momentum for women’s HIV prevention research. It specifically focused on IPM’s most advanced product – the dapivirine ring – and the challenges and obstacles that IPM overcame to develop it.
Print/Digital Media
- Science Speaks Blog: Can a vaginal ring be part of HIV prevention arsenal by 2016?

Social Media
- IPM, other leading women’s health and HIV/AIDS groups (e.g. Women Deliver, IAVI) tweeted about the piece

World AIDS Day (27 November 2013; 1 December 2013)
To mark World AIDS Day, Dr. Zeda Rosenberg authored an op-ed published on Devex highlighting the role of innovation in achieving an AIDS-free generation. She emphasized the need for female-initiated health technologies and a robust pipeline of products that meet individuals’ preferences and help offset the risk of the virus’ resistance. On December 1, IPM released the third and final installment of its Real Voices videos, which featured scientists, clinicians, advocates and community members discussing the potential impact of an effective microbicide.

Print/Digital Media
- Devex: How innovations will pave the way to an AIDS-free generation

Social Media
- IPM and a number of organizations, including AIDS-Fondet and Sex og Politikk, tweeted about the Devex op-ed
- AVAC and Sex og Politikk tweeted about the Real Voices video

2014 Conference on Retroviruses and Opportunistic Infections (4 March 2014)
The Microbicide Trials Network published a press release about new data on the combination dapivirine-maraviroc ring, announced at the 2014 Conference on Retroviruses and Opportunistic Infections (CROI). The press release highlighted the combination ring’s safety but noted that additional research was needed to improve maraviroc’s absorption into tissues. IPM published its own press release on the data (included in the “IPM Public Statements and Messages” document). Media coverage of the data focused on the results of the study and the product’s potential, noting that while it is still in the early stages of development, the combination ring could eventually expand the range of HIV prevention options for women.

Print/Digital Media
- Microbicide Trials Network: First Trial of Combination ARV Vaginal Ring for HIV Prevention Finds Ring Safe but One ARV Carrying the Weight; cross posted on eWallstreeter, First Word MedTech, First Word Pharma, Medical Xpress, Science Codex, Science Daily and Science Newsline
- Fierce Drug Delivery: Study: In two-drug, HIV-preventing vaginal ring, only one drug does the job
- Healio Infectious Disease News: Dapivirine vaginal ring blocked HIV infection in cervical tissue
- UAB News: New method for women’s HIV prevention found to be safe for use

Social Media
- IPM and partners, including AVAC, tweeted about the CROI announcement

58th Session of the UN Commission on the Status of Women (21 March 2014)
IPM launched a new infographic highlighting how women’s HIV prevention and sexual and reproductive health impacts broader global development to mark the final day of the 58th session of the UN Commission on the Status of Women.

Social Media
- IPM promoted the infographic on Twitter, and it was subsequently shared by a number of organizations, including Women Deliver, CAMI and AIDS-Fondet, among others

H. BEST PRACTICES
IPM conducts its research and product development activities in full compliance with regulatory standards as put forth by the US FDA and the European Medicines Agency (EMA), as well as internationally recognized guidelines for GMP, GCP and GCLP, in accordance with the CIOMS. IPM’s research involving animals is contracted to research organizations with laboratories that can provide assurance of compliance with the highest standards for animal care and welfare. IPM contributes to and informs best practices for the field by publishing and presenting its findings in highly-regarded venues (i.e., peer-reviewed journals, international conferences).