Driving Success in Vector Control Product Development for Public Health: The Critical Roles of Preferred Product Characteristics (PPC) and Target Product Profile (TPP) Documents

A Workshop Organized by the
Division of Microbiology and Infectious Diseases
National Institute of Allergy and Infectious Diseases
National Institutes of Health
June 26, July 2, and August 6, 2020

Meeting Report

NIH National Institute of Allergy and Infectious Diseases

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Executive Summary

The goal of the workshop was to understand the critical role of preferred product characteristics (PPCs) and target product profiles (TPPs) in the development of vector control products, and to provide investigators with hands-on experience in developing these documents. Due to the COVID-19 pandemic, the workshop was conducted virtually in three separate sessions: June 26, July 2, and August 6, 2020 (for details, please refer to the Agenda in Appendix 1).

The first two sessions were identical in structure. Single presenters provided an array of perspectives, including science and industry, with Q&As following each presentation. The sessions, which discussed varying aspects and experiences of developing PPCs and TPPs, included the following:

- The Purpose, Development, and Implementation of TPPs for Vector Control Products for Public Health
- Why PPCs and TPPs are Essential – The World Health Organization's (WHO's) Perspective
- Recent Experience with PPC and TPP Development – Investigator's Perspective
- How Modeling Can Inform Product Development
- Stage Gates in the Development of a Novel Vector Control Product
- Killing a Product – What to Look For?

For the third session, participants were instructed to develop PPCs and TPPs for four specified vector control products: repellents, bed net combination insecticides, entomopathogenic fungus, and symbionts. Each team had a designated team leader. There was a Q&A time allotted for these presentations and polling questions posed by co-hosts to encourage discussion.

Throughout the workshop, the importance of the following concepts in developing vector control products was highlighted:

- Stakeholder engagement is critical in securing public acceptance.
- PPC documents should be considered as a helpful framework and valuable overarching document for product development, and can best be viewed as an umbrella, outlining the product development efforts.
- A TPP, unlike a PPC document, is more specific and detailed. It is a living document as it can be revised and updated following critical evaluations of the observations gained during the development process.
- Engagement with regulatory agencies such as the WHO, the U.S. Environmental Protection Agency (EPA), and the U.S. Food and Drug Administration (FDA) early and often during the product development process is important.
- Creating and cultivating cross-functional teams to objectively examine progress against set criteria and implement appropriate stop-and-go gates during product development is essential.
- Pricing is an important factor to be considered. The price should be affordable as most vector products are targeted for low-to middle income countries.

Meeting Summary

Scientific Session, Day 1: Friday, June 26, 2020

Welcome and Introduction (Adriana Costero-Saint Denis and Ghiorghis Ghenbot, NIAID)

Dr. Adriana Costero-Saint Denis welcomed everyone and emphasized the importance of advancing translational research to facilitate vector control product development. Dr. Ghiorghis Ghenbot noted that this was the third workshop in past three years about NIAID's vector control product development initiatives. Previous workshops included "A Primer for the Design and Conduct of Clinical Trials for Vector Interventions" (2018); and "Vector Control Product Development Pathway: Phase-Dependent Evidence Gathering" (2019).

Dr. Ghenbot outlined the goal and the expected outcomes of the workshop. The goal of the workshop was to understand the critical role PPC and TPP documents play in the development of a vector control product. Expected outcomes were that participants: will gain a basic understanding of the elements of PPC and TPP documents; will recognize the value these documents have on streamlining the development process and engaging with partners; and will recognize that a TPP is a living document subject to change as the development process progresses.

Dr. Ghenbot briefly explained the format of the workshop. The first two days featured presentations that focused on the concepts of PPC and TTP and emphasized the importance of understanding where PPC and TPP exist in the continuum of the product development space as efforts move from basic research in the lab and then to the field. The third day featured presentations from team leaders on PPC and TPP documents generated for a specific vector control product.

Dr. Ghenbot then introduced the moderators of the first two presentations: Erika Lindroth, Research Liaison Officer for the Armed Forces Management Board (AFPMB); and Gaby Zollner, Manager of The Deployed Warfighter Protection Program at AFPMB. Both individuals are involved in efforts by the U.S. Department of Defense (DoD) to develop novel tools for vector control and bite protection.

Day 1, Part 1: Speaker Presentations

The Purpose, Development, and Implementation of TPPs for Vector Control Products for Public Health *(Sarah Rees, Innovative Vector Control Consortium (IVCC))*

Dr. Sarah Rees provided insight into how a not-for-profit organization develops a TPP. The IVCC is a not-for-profit organization that is focused on product development partnerships designed to facilitate the development and delivery of new and improved vector control tools to prevent malaria and other neglected tropical diseases.

At IVCC, the development of a TPP is driven by first identifying the need and then identifying the processes and technologies to develop the product. IVCC first creates a Target Candidate Profile (TCP) that reflects the basic research. IVCC makes a distinction between the TCP and a TPP, the latter being created only when they have identified the technology to be used in

developing the product. The terminology and the distinction between TCPs and TPPs can be confusing at times (Burrows et al, Malar J (2017) 16:26). In the development of a TPP, several key questions were considered:

- Intellectual property - new, competitor, or replacement
- Safety and efficacy - potency, formulation, and stability
- Manufacturability - technology to support continued product development and resources
- Route to market - affordability and profitability, approval process, and supply chain

Why PPCs are Essential – WHO's Perspective on Preferred Product Characteristics *(David Schellenberg and Jan Kolaczinski, WHO)*
At the WHO, Dr. David Schellenberg provides support for malaria initiatives, while Dr. Jan Kolaczinski specializes in vector control efforts.

With respect to PPCs and TPPs, WHO is:

- Completing a transformation phase towards the creation of a science division with departments of quality, norms, and standards; this should facilitate the development and review of such documents.
- Working towards reducing the lack of transparency in policy making and inconsistencies in review standards and recommendations.
- Developing PPCs by considering the unmet needs and the types of products that might be coming down the pipeline. This process is believed to increase investment in those areas and to engage product developers, academics, and other researchers to streamline the process of product development and qualification pathways.
- Hoping that PPCs inform developers about the product development process and that meeting PPC requirements reduces, but does not eliminate fully, uncertainty.
- Providing examples of PPCs and TPPs on its website. Some PPCs and TPPs have been developed. While WHO has laid out its own process, it recognizes there may be existing target profiles used to create a PPC (for example https://www.who.int/news-room/articles-detail/public-consultation-on-preferred-product-characteristics-for-malaria-vector-control-interventions).

Discussion *(Moderator: Gaby Zollner, DoD)*
This session took place in the form of Q&A and focused on the preceding presentations. Key elements that were highlighted included:

- WHO is open to and welcomes developer engagement.
- PPCs for vector control product development were not available at the time of the workshop, except in draft form.
- The importance of: identifying the unmet need before investing in developing a product; the availability of appropriate technology to sustain the development of the product; reaching out to WHO before spending resources on product evaluation, and; taking into account acceptability by the end user.

Part 2, Day 1: Speaker Presentations

Recent Experience with PPC and TPP Development - Investigator's Perspective
(Molly Duman-Scheel, University of Notre Dame)
This presentation provided an investigator's perspective on the use and development of a TPP. Dr. Molly Duman-Scheel acknowledged the help provided by IVCC during the development of a TPP for a mosquito larvicide. The investigator discussed studies using yeast interfering RNA larvicide as a bait to kill larvae and adults, an approach that potentially could be used as a new intervention to combat multiple mosquito vectors of human diseases. The hope is that lure-and-kill species-specific tablets may be integrated in mosquito control programs; field studies are ongoing.

Considerable attention during development was given to:

- Mode of action and potential insecticide resistance
- Impact on non-target organisms
- Product formulation, shelf-life, configuration
- Licensing discussions with the EPA
- Consumer engagement, product affordability and acceptability (via surveys/interviews)

Discussion *(Moderator: Erica Lindroth, DoD)*
Questions and responses generally focused on the investigator's interaction with IVCC for the development of a TPP and for the engagement with EPA. The discussion highlighted the benefit of developing a TPP early on, ensuring consumer input, and interacting with the EPA.

Closing Notes: Day 1
Dr. Costero-Saint Denis noted that responses to questions not covered during the participant discussions would be provided via email or through the meeting website link.

Scientific Session, Day 2: Tuesday, July 2, 2020

Welcome and Introduction (Adriana Costero-Saint Denis and Ghiorghis Ghenbot, NIAID)

Dr. Ghiorghis Ghenbot introduced the workshop by first addressing some questions raised during the previous session on the nature of PPCs and TPPs, and on the ownership of such documents. Dr. Schellenberg (WHO) clarified that that a PPC document is a higher-level document outlining the preferred characteristics, whereas the TPP is much more specific, generally created by someone directly involved in developing that product. Furthermore, it was noted that WHO owns PPCs, and the sponsor owns TPPs. However, there is a partnership between the two. The WHO maintains the PPCs and TPPs that it publishes in its public website (e.g., https://www.who.int/publications/i/item/9789240018754).

Dr. Ghenbot then introduced the moderator for the next series of presentations: Dr. Helen Jamet, Deputy Director, Vector Control for the Malaria Team, the Bill and Melinda Gates Foundation (BMGF).

Part 1, Day 2: Speaker Presentations

How Modeling Can Inform Product Development *(Melissa Penny, Swiss TPH)*
Dr. Melissa Penny discussed how modeling can be useful in vector control product development, and how modeling can be used as an iterative process to evaluate and refine the elements covered in a TPP. This process, while mostly starting with existing data, should be augmented with evidence from new findings. The use of modeling in integrating information on parasite density and the mosquito lifecycle and in describing disease progression in humans was highlighted. Examples of collaborative work with IVCC and the Gates Foundation were provided.

Stage Gates During the Development of a Novel Vector Control Product *(Kendra Lawrence, Department of Defense)*
The use and practice of the stage gate process is well practiced in the pesticide industry but not in vector control product development. Dr. Kendra Lawrence's presentation focused on defining decision points along a product development process where there is a need to consider the progress achieved against the milestones set. It was emphasized that the actions taken should be based on evidence. Implementation of stage gates ensures a more effective allocation of resources and avoids scope creep, minimizing waste, and effective communication with stakeholders. The stage gate process is better established when cross-functional teams have been involved in developing a TPP as a living document. Two examples (bed nets and repellents) were discussed.

Killing a Product – What to Look For *(Melinda Hadi, Vestergaard)*
Dr. Melinda Hadi discussed the value of WHO PPCs as a means of identifying potential unmet public health needs and of a TPP as a comprehensive internal guide for continued engagement with the EPA or WHO. Unlike in the vector control product development area, it was noted that there are well-established and generic risk assessment models for safety and regulatory issues for chemical-based control approaches. One of the case studies presented was on insecticide-treated plastic sheeting for displaced populations, such as for refugees, temporary laborers, and individuals seeking shelter. The other case presented was on non- mesh long-lasting netting. In both cases, criteria developed in the respective TPP, along with careful evaluation of the observation gained from end users and similar products in the market, were used to determine the risk and viability of the projects.

Discussion *(Moderator: Helen Jamet, BMGF)*
The discussion was conducted in Q&A format. It centered on two main topics: the development and use of TPP and modeling.

A TPP is valuable as it summarizes the scientific, regulatory, and commercial aspects of the product. Investing time in developing a TPP early on during the development of a product is very worthwhile. Moreover, once a TPP has been validated through development and marketing for a given product, it can serve as a reference for other targets, including research proposals.

Regarding mathematical modeling during product development, participants noted the paucity of information on vector control products. This should not be an impediment to considering mathematical modeling during product development. For example, investigators can start with

input from experts and refine the model as needed. However, it was noted that this could be computationally intensive and require resources and collaborators.

Following the discussion session, Dr. Ghenbot briefly described the format and content for the third and final session of this workshop in August. Four teams, each with a designated team leader, would present their draft PPC and TPP documents on four different vector control products and describe the challenges faced in developing the documents. He discussed new WHO guidance document that could be helpful in finalizing their draft documents.

Team Presentations Session, Day 3: Thursday, August 6, 2020

Team Presentation Summaries

This session comprised presentations from four different teams:

- Team A: Repellent
- Team B: Bed Net Combination
- Team C: Entomopathogenic Fungus
- Team D: Symbionts

During the third and final session of the workshop, there were four presentations, with each team instructed to develop a PPC and TPP for a specific vector control approach. Teams had roughly four weeks in advance to work on these documents, with team leaders coordinating the efforts. There was a Q&A session and discussion at the end of each team presentation.

The teams and products each team was assigned to work on are included in Appendix 4.

Final Discussion *(Moderators: Ghiorghis Ghenbot, NIAID; Gabriela Zollner, DoD; Helen Jamet, BMGF)*

At the close of the workshop, several questions were raised for discussion. Below is a summary response to each of the questions raised.

What happens with PPCs/TPPs as product evaluation and development advances?
PPCs developed by the WHO incorporate the perspective of the WHO and front-line users and outline the envisioned requirements for the product category. These documents act as guidance for innovators who are developing products for vector-borne diseases. A TPP is a living document; a roadmap that captures technical and business development goals. It captures the expectations of stakeholders. It must be robust and incorporate the needs of all partners. The development activities should accurately reflect the field outcomes. As such, investigators should be flexible and adjust expectations in view of the actual field observations gathered during product development. Furthermore, the observations will help decide go/no-go decisions for properly managing the development task.

How should we define the standards for minimum stakeholder acceptance – and who is responsible for compiling data, updating on minimal/optimal thresholds across TPPs for a single product category?

When defining the standards, it was suggested that along with the intended use, investigators need to consider how a new strategy complements existing methods of control (if any), and to incorporate community acceptance at local, regional, and national levels. This would assist in making the deployment process feasible. The innovator is ultimately responsible for designing, updating, and maintaining a TPP. Depending on the intended use, regulatory agencies, including the FDA and the EPA, should be involved in standardizing the requirements and establishing clear protocols as the research moves from lab to testing. The EPA is working on specific guidelines for facial repellents. The EPA encourages innovators to meet with the agency early in the process. This is also the case for FDA.

What regulatory standards/agencies are appropriate, especially for first-in-class products, and in locations where appropriate regulatory bodies for reviewing new technologies do not exist?
The WHO determines if the product class is a new or established class. Requirements by other regulatory agencies should be adhered to. The WHO recognizes the lack of experienced local regulators and stressed the importance of innovators collaborating with the WHO as a new product class moves through the process. Moreover, WHO has different departments that work at the different stages of product development.

Workshop Conclusion

Dr. Costero-Saint Denis expressed her hope that this workshop expanded participants' understanding of the importance of PPCs and TPPS, increased contact networks, and provided opportunities for collaboration, and that the team exercise drafting PPCs and TPPs were helpful.

She closed the meeting by thanking everyone involved in these sessions – the speakers, moderators, the team leaders and team members, NIAID MEET technical support staff, and the participation of agencies including the WHO, EPA, and FDA.

Appendix 1: Workshop Agenda

Driving Success in Vector Control Product Development for Public Health: TheCritical Role of Preferred Product Characteristics (PPC) and Target Product Profiles (TPP)

Objectives:

- To understand the critical role of preferred product characteristics (PPCs) andtarget product profiles (TPPs) in the development of vector control products.
- To provide investigators with hands-on experience in developing these documents.

Friday, June 26, 2020

Time*	Activity	Speaker
10:00 AM	Welcome/Introduction	Adriana Costero-Saint Denis/GhiorghisGhenbot, NIAID
10:15 AM	The Purpose, Development, and Implementation of TPPs for Vector Control Products for Public Health	Sarah Rees, IVCC
10:45 AM	Why PPCs are essential - WHO's perspective	David Schellenberg & Jan Kolaczinski, WHO
11:00 AM	Discussion	ALL Participants (**Lead: Gaby Zollner,DoD**)
11:30 AM	Recent Experience with PPC and TPP Development - Investigator's Perspective	Molly Duman Scheel, Univ. of Notre Dame
11:45 AM	Discussion	ALL Participants (**Lead: Erica Lindroth,DoD**)
12:00 PM	Adjourn	

Thursday, July 2, 2020

Time*	Activity	Speaker
10:00 AM	Welcome/Introduction	Adriana Costero-Saint Denis/GhiorghisGhenbot, NIAID
10:15 AM	How modeling can inform product development	Melissa Penny, Swiss TPH
10:30 AM	Stage Gates in the Development of a Novel Vector Control Product	Kendra Lawrence, DoD
10:45 AM	Killing a product – what to look for	Melinda Hadi, Vestergaard

11:00 AM	Discussion	ALL Participants (**Lead: Helen Jamet,BMGF**)
11:30 AM	Preparation for August meeting	Ghiorghis Ghenbot, NIAID
12:00 PM	Adjourn	

Thursday, August 6, 2020

Time*	**Activity**	**Speaker**
8:45 – 9:45 AM	*Team rooms available for final discussions/prep (optional)*	
9:30 – 9:45 AM	*Team leaders test presentations (optional)*	
10:00 AM	Welcome & Introduction	Ghiorghis Ghenbot/Adriana Costero-SaintDenis, NIAID
10:10 AM	Team A: Repellent	Presentation (PPC/TPP – 20 minutes) Discussion (10 minutes) (**Lead: GhiorghisGhenbot, NIAID**)
10: 40 AM	Team B: Bed Net Combination	Presentation (PPC/TPP – 20 minutes) Discussion (10 minutes) (**Lead: EricaLindroth, DoD**)
11:10 AM	Break (10 minutes)	
11:20 AM	Team C: Entomopathogenic fungus	Presentation (PPC/TPP – 20 minutes) Discussion (10 minutes) (**Lead: GhiorghisGhenbot, NIAID**)
11:50 PM	Team D: Symbionts	Presentation (PPC/TPP – 20 minutes) Discussion (10 minutes) (**Lead: EricaLindroth, DoD**)
12:20 PM	Final Discussion	**Leads: Ghiorghis Ghenbot, NIAID; Gabriela Zollner, DoD; Helen Jamet, BMGF**
12:50 PM	Next Steps	Adriana Costero-Saint Denis, NIAID
1:00 PM	Adjourn	

Appendix 2: Participant List

Last Name	First Name	Affiliation
Abdoulaye	Diabate	Centre Muraz, Burkina Faso
Achee	Nicole	University of Notre Dame
Alphey	Luke	The Pirbright Institute, UK
Armistead	Jennifer	US Agency for International Development (USAID)
Carr	Ann	Vanderbilt University
Catteruccia	Flaminia	Harvard University
Chitale	Rohit	The Defense Advanced Research Projects Agency (DARPA)
Dimopoulos	George	Johns Hopkins University
Dobson	Stephen	MosquitoMate
Duman Scheel	Molly	University of Notre Dame
Elman	Noel	GearJump
Farlow	Robert	Consultant
Garver	Lindsey	Department of Defense (DoD)
Gimnig	John	Centers for Disease Control and Prevention (CDC)
Hadi	Melinda	Vestergaard
Hill	Catherine	Purdue University
Hutter	Audrey	Bill & Melinda Gates Foundation
James	Stephanie	Foundation for the National Institutes of Health (FNIH)
Jennings	Susan	Environmental Protection Agency (EPA)
Koh	Cassandra	Institut Pasteur, France
Kolaczinski	Jan	World Health Organization (WHO)
Lampe	David	Duquesne University
Lawrence	Kendra	Department of Defense (DoD)
Lenhart	Audrey	Centers for Disease Control and Prevention (CDC)
Macdonald	Michael	Consultant
Miller	Kristina	The Defense Advanced Research Projects Agency (DARPA)
Moorthy	Vasee	World Health Organization (WHO)
Moussa	Laura	Food and Drug Administration (FDA)
Norton	Larry	Innovative Vector Control Consortium (IVCC)
Paton	Douglas	Harvard University
Penny	Melissa	Swiss Tropical and Public Health Institute
Rasgon	Jason	Pennsylvania State University
Rees	Sarah	Innovative Vector Control Consortium (IVCC)
Saleh	Carla	Institut Pasteur, France
Saunders	Jennifer	Environmental Protection Agency (EPA)
Schellenberg	David	World Health Organization (WHO)
Scott	Nicole	Cybele Microbiome
Skinner	Anna	The Defense Advanced Research Projects Agency (DARPA)

Last Name	First Name	Affiliation
St. Leger	Raymond	University of MD, College Park
Stevenson	Jennifer	World Health Organization (WHO)
Stillwaugh	Virna	Environmental Protection Agency (EPA)
Van De Wyngaerde	Marshall	DoD/Walter Reed Army Institute of Research (WRAIR)
St. Leger	Raymond	University of MD, College Park
Stevenson	Jennifer	World Health Organization (WHO)
Stillwaugh	Virna	Environmental Protection Agency (EPA)
Van De Wyngaerde	Marshall	DoD/Walter Reed Army Institute of Research (WRAIR)
Zamisch	Monica	The Defense Advanced Research Projects Agency (DARPA)
Zwiebel	Laurence	Vanderbilt University

Appendix 3: Workshop Organizers

Last Name	First Name	Affiliation
Costero-Saint Denis	Adriana	National Institute of Allergy and Infectious Diseases (NIAID)
Ghenbot	Ghiorghis	National Institute of Allergy and Infectious Diseases (NIAID)
Barsaku	Venera	National Institute of Allergy and Infectious Diseases (NIAID)
Lindroth	Erica	Department of Defense
Zollner	Gabriela	Department of Defense
Jamet	Helen	Bill & Melinda Gates Foundation
Malone	David	Bill & Melinda Gates Foundation

Appendix 4: Teams, Team Leads and Products

Team	Product	Name	Organization
A	REPELLENT	**Nicole Achee (lead)**	University of Notre Dame
		Nicole Scott	Cybele Microbiome
		Jennifer Saunders	EPA
		Lawrence Zwiebel	Vanderbilt University
		Noel Elman	JumpGear
		Michael McDonald	Consultant
		Kendra Lawrence	DoD
B	BED NET COMBINATION INSECTICIDE	**Sarah Rees (lead)**	IVCC
		Flaminia Catteruccia	Harvard University
		Jason Rasgon	Penn State University
		Melinda Hadi	Vestergaard
		Lindsay Garver	DoD
		John Gimnig	CDC/PMI
		Jennifer Armistead	USAID
C	ENTOMO-PATHOGENIC FUNGUS	**David Malone(lead)**	BMGF
		Raymond St. Leger	UMD, CollegePark
		Catherine Hill	Purdue University
		Melissa Penny	Swiss TPH
		Stephanie James	FNIH
		Larry Norton	IVCC
		Rohit Chitale	DARPA
D	SYMBIONTS THAT INTERRUPT TRANSMISSION	**Molly Duman-Scheel (lead)**	University of Notre Dame
		Stephen Dobson	MosquitoMate
		George Dimopoulos	Johns Hopkins University
		David Lampe	Duquesne University
		Marshall Van DeWyngaerde	DoD/WRAIR
		Audrey Lenhart	CDC
		Laura Moussa	FDA

Appendix 5: List of Relevant Publications

- Update on recent, ongoing and future GMP work on malaria entomology and vector control. February 5, 2020, Global Malaria Program/WHO: https://endmalaria.org/sites/default/files/u224/1_Jan%20Kolaczinski.pdf
- The Importance of Vector Control for the Control and Elimination of Vector- Borne Diseases. January 16, 2020, PLoS NTD: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6964823/pdf/pntd.0007831.pdf
- WHO Target Product Profiles, Preferred Product Characteristics, and Target Regimen Profiles: https://www.who.int/observatories/global-observatory-on-health-research-and-development/analyses-and-syntheses/who-r-d-blueprint/who-target-product-profiles
- Report of the Eleventh Meeting of the WHO Vector Control Advisory Group. Nov. 11-13, 2019, WHO https://www.who.int/publications-detail-redirect/9789240000759
- WHO Prequalification Team: Vector Control Products: https://www.who.int/pq- vector-control/en/
- The evaluation process for vector control products. June 2017, WHO https://apps.who.int/iris/bitstream/handle/10665/255644/WHO-HTM- GMP-2017.13-eng.pdf
- Simplifying and Clarifying Vector Control Product Listing and Policy Guidance. May 14, 2018, https://www.who.int/vector-control/vcag/vcag-may2018-i2i-presentation.pdf?ua=1.
- Integrating Vector Control Across Diseases. October 1, 2015, BMC Medicine: https://bmcmedicine.biomedcentral.com/track/pdf/10.1186/s12916-015-0491-4.pdf