Proven Efficacy & Public Health Value: Eligibility of Biopesticides for the Vector Expedited Review Voucher (VERV)

April 2024

Nick Hamon[1]
Daniel Markowski[2]
Jeffrey Moe[3]
Derric Nimmo[4]

[1] Nick Hamon, PhD is the former CEO of the Innovative Vector Control Consortium and co-author of the 2017 Health Affairs paper advocating for the creation of the Vector Expedited Review Voucher
[2] Daniel Markowski, PhD is Technical Advisor, American Mosquito Control Association
[3] Jeffrey Moe, PhD is a Duke University faculty member, co-author of the 2017 Health Affairs paper advocating the creation of the Vector Expedited Review Voucher, and co-author of the 2006 Health Affairs paper advocating the creation of FDA's Priority Review Voucher Program
[4] Derric Nimmo, PhD is the Director of Technical Development at the Innovative Vector Control Consortium

Context

The Vector Expedited Review Voucher (VERV) program was enacted as part of the 2022 Presticides Registration and Improvement Act (PRIA 5) and must be re-authorized in PRIA 6 (~ 2027). The current authorization requires EPA to report on VERV awards, redeemed vouchers and expediting performance. If no VERV are awarded during the current authorization, Congress will have no evidence to support continuation of the VERV program.

Registrants face significant disincentives to invest in public health use insecticides. VERV creates financial value by monetizing speed to market in a voucher. VERV value offsets some of the losses created by investing in public health use insecticides. The value of a voucher is sensitive to supply and demand: if many vouchers are awarded the value of the voucher will decrease. We have observed voucher value reductions in FDA's Priority Review Voucher program when the eligibility criteria were expanded and many more PRV were awarded. We also note that when many vouchers are awarded, it increases the burden on agencies when more awarded vouchers are redeemed.

EPA provided guidance to registrants in December 2023 regarding VERV. Frequently the agency selected a "case by case" approach to determine eligibility. As each eligibility decision is made it creates a precedent. VERV registrants will expect consistency among those precedents. The consistent application of overarching principals based upon the "letter and spirit" of the VERV-enacting legislation must guide case by case decisions; principals should be communicated to registrants as they are applied and evolve.

The VERV legislation gave EPA discretion to make products eligible that have proven efficacy and create public health value. The authors offer the following opinions regarding biopesticide eligibility at the request of the agency.

Vector control to Reduce Disease Transmission

Vector control using insecticides is a proven method to reduce disease transmission. However, vector control strategies need interventions or a combination of interventions that protect humans against different groups of vectors, in different transmission settings (or contexts), different human populations, or via a different mechanism compared to existing methods. The development of novel insecticide active ingredients and products supports the fight to address insecticide resistance.

Target Product Profiles in Malaria Products Suggest Important Capabilities for New Vector Control Products

Malaria has the highest human burden of all global vector-borne diseases. Effective malaria vector control has historically relied on methods that address indoor feeding and/or indoor resting mosquitoes through Indoor Residual Spraying and Insecticide Treated Mosquito Nets. In additional specific situations, there are methods for controlling vectors in their immature stages in their aquatic habitats. Other mosquito control tools include aerial spraying, attractive targeted sugar baits, and spatial repellents. The "target product profiles" of proven, effective adult mosquito insecticides generally describe synthetic pyrethroid levels of potency, no cross-resistance with insecticide-resistant mosquito strains, the ability to formulate and deliver on multiple surfaces such as polymer nets and walls, rapid knockdown and speed of kill, long residual efficacy (photostable) and low cost of goods that allow for affordability in the target markets.

Public Health Value

- The VERV program was created to raise awareness of the need for new and effective vector control tools and reward innovators for investing in public health product development.
- To receive a VERV novel products need to demonstrate *public health value* which is not defined in the authorizing legislation. The World Health Organization offers this definition: "A product has Public Health Value if it has proven protective efficacy to reduce or prevent infection and/or disease in humans".
- An effective public health product will have a significant impact on human populations as well as on individuals.
- Products with significant public health value typically target vectors and diseases for which no effective cure or treatment is currently available or for which insecticide resistance is reducing the impact of existing tools.
- An important goal of the VERV program is to encourage the discovery and development of replacements for pyrethroids in insecticide-treated bed nets which have been the mainstay of malaria control in many countries throughout the world. An effective bed net will have up to three years of efficacy and significant wash-off resistance as well as high stability and durability.

VERV Eligibility Criteria

- Prevents, mitigates, destroys or repels pyrethroid or other insecticide-resistant mosquitoes, with a novel or unique mechanism or mode of action, different from other insecticides already registered by the Administrator for mosquito control; targets mosquitoes capable of spreading such diseases as malaria, dengue, zika, chikungunya, St. Louis encephalitis, Eastern encephalitis, Western encephalitis, West Nile encephalitis, Cache valley encephalitis, La Crosse encephalitis, and yellow fever.

    - The “different from already registered” requirement may be waived if the Agency determines there is a significant public health benefit. Waiver requests must be submitted with the application and decisions will be made on a case-by-case basis.
- Demonstrates a proven efficacy (performance) against pyrethroid or other insecticide-resistant mosquitoes. EPA will evaluate these studies and ensure efficacy data meet the same requirements required for other products intended for mosquito control.
    - Efficacy studies along with resistant ratio determinations of the resistant mosquito strain must be submitted to fulfil product performance requirements.
    - On a case-by-case basis, EPA may accept a rationale for efficacy based on the active ingredient’s novel mode of action to demonstrate control of insecticide-resistant mosquitoes. EPA will evaluate these studies and ensure efficacy data meet the same requirements required for other products intended for mosquito control.
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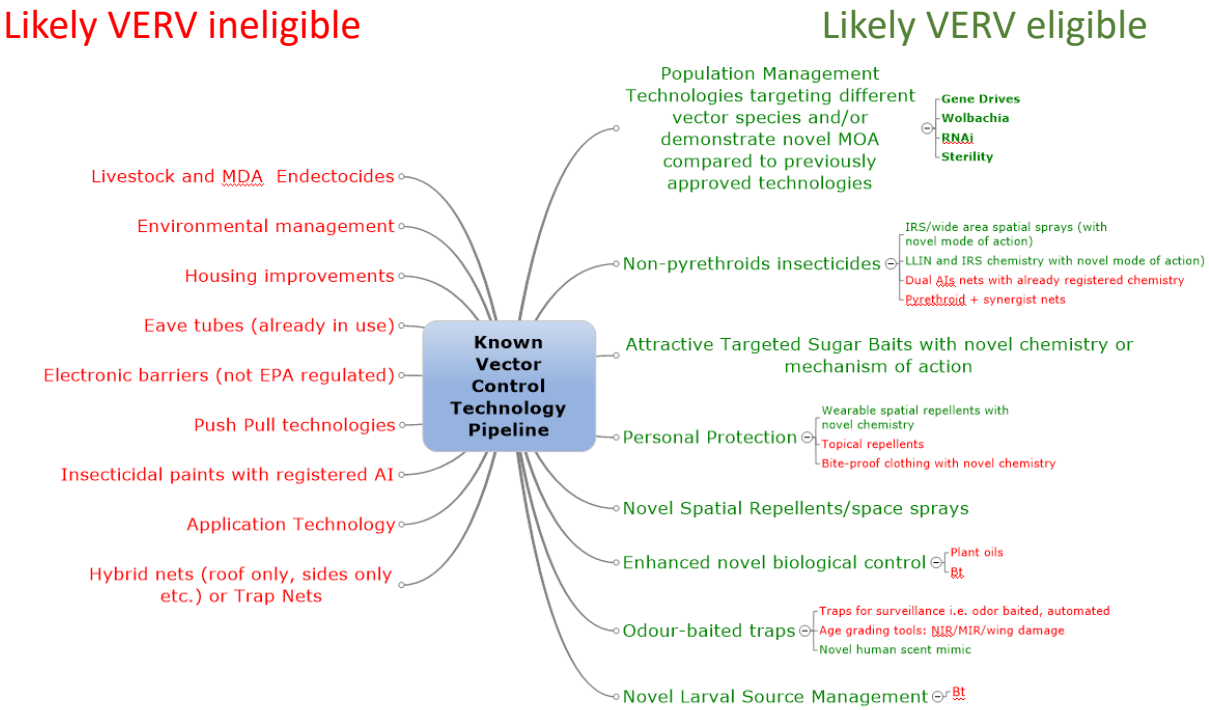
- Broadens the adoption of integrated pest management strategies, such as insecticide resistance management, or makes those strategies more effective.
- Is not contained in any pesticide product registered by the Agency as of the date of the enactment of the Pesticide Registration Improvement Act of 2022 or does not contain an active ingredient approved in the 2-year period preceding the date of registration by any global stringent regulatory authority for the same uses, vectors, and applications.
- EPA will determine if an application has a unique or novel mode of action on a case-by-case basis. The agency considers factors including:
    - Mechanism of action that targets new or different receptors,
    - Pesticide is in a new or different chemical class (including classification by the Insecticide Resistance Action Committee),
    - Mechanism of action uses special approach such as interrupting behavior, targeting different life stages, or prohibiting reproduction,
    - Live release control techniques should target a specific species not controlled by another live-release product.
- There have been detections of mosquito-borne disease and associated deaths in the United States and its territories, the detections have increased, or there is a threat of a new mosquito-borne disease emerging in the United States or its territories.
- Novel products must be made accessible for use in the United States, including territories or possessions of the United States, and countries where mosquito-borne diseases, such as malaria, are prevalent. The VERV application must include a global access plan that will be made publicly available for the active ingredient and that addresses: a) manufacturing locations, including any licensed third-party manufacturers; b) distribution and procurement processes for malaria vector control programs in selected countries and c) the prices for common quantities of the product.

- A repurposed agricultural active ingredient should have a different mode of action than other products currently registered in the United States and its territories to address mosquito resistance and broaden Integrated Pest Management (IPM) and/or Insecticide Resistance Management (IRM).
- The re-purposed agricultural active ingredient should be novel to mosquito vector control in the United States and its territories and appropriate for outdoor use (e.g., larvicides, adulticides, attractive treated sugar baits) or for use in primary indoor malaria vector control intervention areas, including indoor residual sprays (IRS), insecticide-treated nets (ITNS) and other effective interventions.
- The re-purposed agricultural active ingredient is unconditionally registered with the U.S. EPA and meets all safety standards for human and environmental health.

The VERV Eligibility Criteria can be Summarized as a Decision Tree (Figure 1).

The Currently Understood Universe of Mosquito Control Innovations Many mosquito control innovations are currently being developed. Some of these innovations are designed to create public health value while others have very limited or no uses to protect humans from vector-borne diseases. Using available information, we analysed the currently known innovation landscape (Figure 2) applying the VERV eligibility criteria to determine those innovations which are likely eligible for a VERV; others which fail on one or more of the criteria and therefore are likely ineligible.

Figure 2. Currently Known Mosquito Control Innovation Universe



Production management targeting different vector species and/or demonstrate novel MoA compared to previously approved technologies (depicted top right green in the preceding Mosquito Control Innovation Universe graphic)

The diagram below (Figure 3) applies a targeted MoA/species eligibility principal to selected non-insecticidal novel products. Because these products have novel and/or nuanced mechanisms of action, they are not easily classified into a specific IRAC category. Because the EPA can, at its discretion, determine that a novel mechanism or mode of action has a significant public health value, we advise the agency exercise restraint and selectively award the VERV incentive to live release products with a novel mechanism of action in a new species rather than repeated use of the same species for multiple strategies.[5] The targeted MoA/species eligibility principal can be reviewed and revised later during the current authorization or after re-authorization in PRIA 6 (~ 2027).

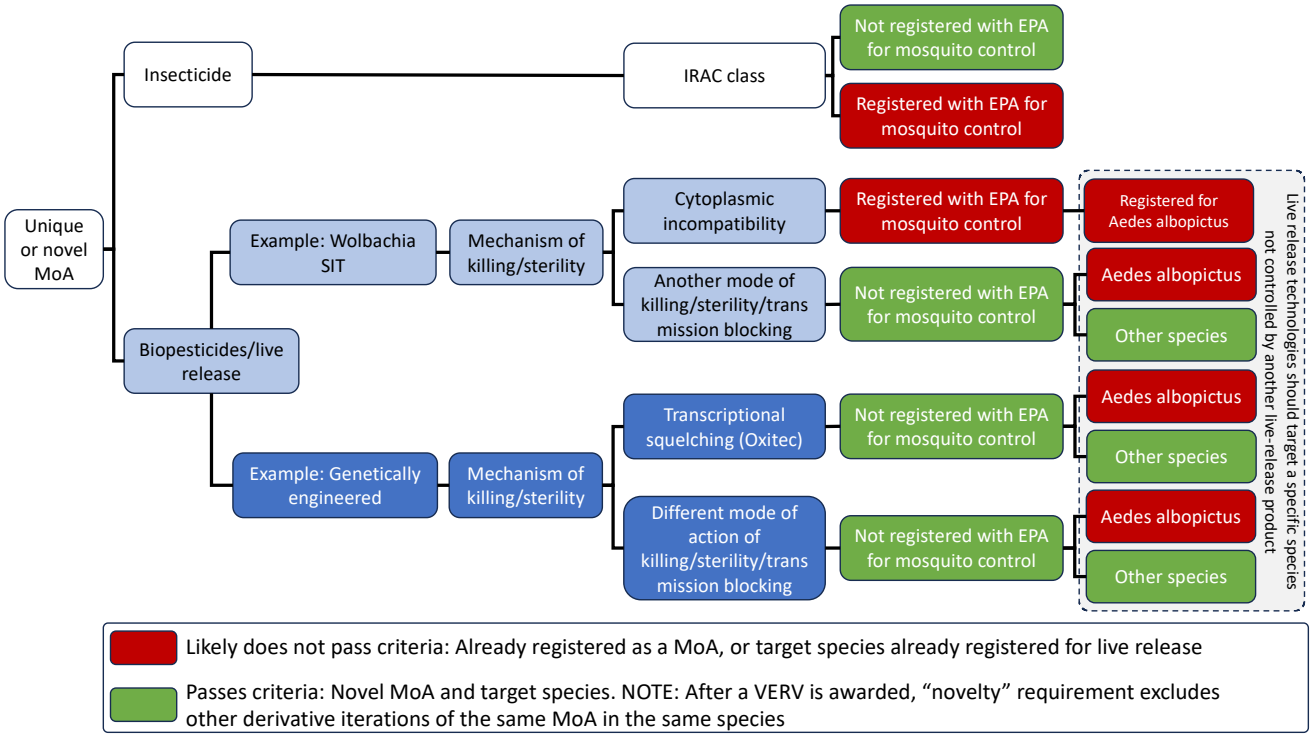


Figure 3. Diagram depicting eligibility criteria for representative modes of action.

<u>Wolbachia</u>

Wolbachia has been used around the world for population replacement: the strain blocks the transmission of dengue fever in humans. A second *Wolbachia* approach is population

[5] In December 2023 FDA denied Bluebird Bio a Priority Review Voucher for Lyfgenia® (lovotibeglogene autotemcel) because the agency had previously awarded a voucher to Zynteglo® (betibeglogene autotemcel): both products use the same lentiviral vector and gene payload technology. FDA demonstrated a targeted eligibility strategy that awards one voucher, rather than multiple vouchers, for products that use the same gene technology with minor changes.

suppression where *Wolbachia* is used to prevent offspring from surviving through cytoplasmic incompatibility. These represent two different modes of action. The mode of action for population suppression is known; but preventing dengue transmission is not. In summary:

- *Wolbachia* for population suppression in *Ae. albopictus* has been registered with the EPA and, therefore, fails on the "novelty eligibility criteria" (not previously registered) and is ineligible for VERV.
- Agency-registered *Wolbachia* SIT has only been applied to date for the *Aedes* species. If developed in other species, we consider it ineligible because it uses the same mode of action (cytoplasmic incompatibility).
- However, if *Wolbachia* could be developed for *Anopheles* species to block malaria transmission, it would represent a new mode of action in a new species. In our analysis, this is a new mode of action in a new species not previously registered with a stringent regulatory authority and, therefore, potentially eligible for VERV.

Genetically Engineered products

Transgenic approaches for mosquito control can also include multiple mechanisms or modes of action, including population modification to block transmission and population suppression. A representative example of the latter is Oxitec's transgenic mosquitoes, which are engineered with a synthetic genetic sequence that kills most of the mosquitoes carrying the trait through transcriptional squelching.

- No genetically engineered mosquito control techniques have received full EPA registration; therefore, any live release transgenic mosquito product would be VERV eligible: if it is operational on a new species without a previously registered live release product.
- When a second genetically engineered mosquito is developed, it would first need to be determined that it represents a novel mode of action. For example, the gene causes lethality by a different mode of action than transcriptional squelching. Then, it would need to be developed in a new species not previously registered with another live-release product.

RNAi products

Double-stranded RNA-mediated gene silencing (RNAi) has been demonstrated to target specific proteins within certain insect species. In particular, RNAi technology can be used to target chitin production in mosquitoes. If this technology could be developed in a safe, sustainable approach, it could provide a novel mechanism of action to suppress mosquito populations that exhibit insecticide resistance.

- RNAi must be stabilized and survive for an appropriate amount of time, determined by the vector control tool application (see stability section below).
- RNAi technologies can be targeted to a variety of different essential proteins in the organism; designed to produce insecticide-like effects, such as rapid kill.

- It is less likely RNAi products can be made stable enough for bed net/IRS products but could be made into products for sugar baits and possibly larvicides, which would be VERV-eligible.

Stability

Stability is an important product characteristic that greatly contributes to public health value. The criteria for stability will depend upon the type of product, the active ingredient, the target vector and the environmental conditions. For example, the minimum level of stability for an indoor residual spray product for malaria vector control is an average mosquito season, which is generally 4-6 months. For nets, the minimum level of stability is 20x washes and accelerated storage stability at elevated temperatures for 2 years; allowing a net to last 3 years under field conditions. An additional component of stability is the ability of a novel product to remain shelf stable for delivery as part of the product's global access plan. We note that aerial spraying imposes unique stability considerations to balance efficacy with risk-reduction.

If a product has a very short half-life or cannot survive the rigors of transportation and release it may fail to create public health value and should not be VERV eligible.

Conclusion

VERV was enacted to stimulate innovation in vector control for human diseases. The universe of mosquito control innovations will grow as new technologies are discovered, markets for new technologies are expanded and incentives like VERV stimulate research and development. EPA has broad discretion to make innovative technologies eligible for the new VERV incentive. We urge the agency to make the demonstration of public health value a key criterion for evaluating the eligibility of new technologies for the VERV award. By applying a targeted MoA/species eligibility principal to live release and other biopesticide technologies, we believe vector-borne disease patients, the public and the U.S. government will benefit by the achievement of these important aims:

- VERV are likely awarded during the current authorization period,
- eligibility determinations are guided by principals that encourage targeted novel uses and are communicable to registrants.