1. Executive summary

The World Health Organization (WHO) recommends tools, technologies and approaches for use in public health based on demonstrated evidence of their impact on diseases, as well as their safety and quality. The WHO process for evaluating vector control products has been revised in order to better meet the needs of countries endemic for, or at risk of, vector-borne diseases. Under the revised process, the evaluation pathway to be followed is determined by whether or not a product is part of a product class with an existing WHO policy recommendation (1).

Products covered by an existing WHO policy recommendation will follow the Prequalification Pathway, while all new tools, technologies and approaches will follow the New Intervention Pathway, supported by the Vector Control Advisory Group (VCAG). VCAG will validate whether the intervention under assessment has public health value. Once public health value has been demonstrated, WHO will issue a policy recommendation.

On the basis of a request from the Malaria Policy Advisory Committee (MPAC) in March 2017, WHO is reviewing the data requirements associated with the evaluation of new vector control interventions in order to ensure that new interventions can be deployed as soon as possible, while ensuring that the policy recommendations guiding deployment remain evidence-based.

With the move to a revised evaluation system (2) and the arrival of new products, WHO must also guide the assessment of products that clearly fall under an established intervention class, but that differ in their product specification and/or differ from the first-in-class product for which epidemiological data are available. Examples of such new products include mosquito nets treated with a pyrethroid and the synergist piperonyl butoxide (PBO), new indoor residual spray (IRS) chemistries, and new mosquito larvicides and space spray products. For such products, WHO requires reassurance of similar performance (in terms of disease or vector control) in order to provide normative guidance to vector control programmes faced with the challenge of selecting reliable products.

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1 A product has public health value if it has proven protective efficacy to reduce or prevent infection and/or disease in humans.
To discuss these topics in detail and to provide recommendations to MPAC and WHO, an Evidence Review Group (ERG) was convened on 12–14 September 2017. The ERG was tasked with reviewing summarized laboratory and field trial data for selected new vector control products and using these as case studies with which to develop both product-specific policy recommendations and general recommendations on the evaluation of new vector control tools, technologies and approaches.

The product-specific and general recommendations will be published as a WHO recommendation following endorsement by MPAC.

2. Background

The WHO process for the evaluation of vector control products has been revised to better meet the needs of countries endemic for, or at risk of, vector-borne diseases. The revised process came into effect on 1 January 2017 and is designed to accelerate product evaluation to support the continued scale up of core malaria vector control interventions, to strengthen vector control for neglected tropical diseases, and to address key challenges, such as emerging vector resistance to insecticides.

The key objectives of the revised process are to:

1. Enable access to safe, effective and high-quality vector control products;
2. Enhance evidence-based guidance to promote best use and management of vector control tools, technologies and approaches;
3. Promote product quality throughout the product’s life cycle.

Under the revised process, the evaluation pathway to be followed is determined by whether or not a product is part of a product class with an existing WHO policy recommendation. A policy recommendation is a position statement or recommendation issued by WHO, the most recent of which takes precedence over any previously issued recommendation.

Following a request from MPAC, WHO is investigating whether the data requirements for evaluating new vector control interventions can be minimized in order to enable rapid deployment of new technology; at the same time, policy recommendations to guide deployment must remain evidence-based and justifiable. Data requirements to support WHO policy development could potentially be reduced for products that have a similar entomological effect to products in an existing product class, but that belong to a new chemical class not currently covered by the policy. For IRS, for example, products are evaluated based on the percentage kill of the vector (in experimental huts, on well-characterized strains, and in large-scale field trials, on well-characterized wild vector populations) at specific time points following the vector’s exposure to the insecticide and on the duration of residual efficacy on common wall materials (cement, mud and wood). If a new product performs similar to or better than the IRS products currently covered by WHO policy in terms of its residual effect on wild or colony strains and performs equally or better on wild flying vectors, it may be assumed that the new product’s epidemiological impact should be at least as good as that of the comparator products. It could then be argued that the existing WHO policy recommendation for IRS could be extended to the new product, provided it meets some essential efficacy and performance criteria (as currently
defined by WHO guidelines for testing different classes of vector control products covered by WHO policy), and has passed risk assessment for safety. This principle would allow the new product’s deployment on the proviso that it is accompanied by the collection of epidemiological data to confirm the assumption of its epidemiological impact. To discuss these issues in more detail and to provide recommendations on the data requirements and methodology needed to support an extension of the existing policy, WHO convened an ERG to study the available data for a specific IRS product – SumiShield® 50WG. In part 1 of the meeting, the ERG deliberated on this IRS product.

With the increased development of new products to add to the “toolbox” needed to solve many vector control challenges, WHO must also guide the assessment of products that clearly fall under an established intervention class, but that differ substantially in their design from the first-in-class product(s) for which epidemiological data are available. An example of this is the case of mosquito nets treated with a pyrethroid and the synergist PBO, referred to as pyrethroid-PBO nets. While some epidemiological data on impact are available for one product in this class, namely the Olyset Plus net produced by Sumitomo Chemicals Co. Ltd, four other products are available in this class, but they all differ from Olyset Plus in terms of their design. Key differences between products are the location of the PBO (e.g., in all panels of a bed net or just the top panel), the PBO loading dose, the wash retention of the PBO and its bioavailability over a period of time.

Generating new epidemiological data to demonstrate impact on disease is likely to be impractical for such new products entering an existing class, but reassurance of similar or superior performance is nevertheless required in order to provide normative guidance to vector control programmes faced with the challenges of selecting reliable products.

The ERG discussed this topic in more detail in part 2 of the meeting, with the aim of providing advice to WHO on the data requirements and methodology needed to determine whether products entering an established class have similar performance to the first-in-class product.

In part 2, the ERG also discussed the evaluation of larvicides and space spray products, which raise similar questions.

3. Meeting objectives

Part 1

1. To advise WHO on the data requirements and methodology needed to determine whether the existing WHO policy for a class of products can be extended to a new vector control product that is not part of the class, but for which entomological effects are sufficiently similar, in order to facilitate deployment.

2. To apply criteria formulated under objective 1 to the assessment of SumiShield® 50WG, and to advise WHO on whether current policy recommendations for IRS products should be extended to this new insecticide and, if so, whether there should be conditions associated with the extension of the policy.
Part 2

3. To advise WHO on the data requirements and methodology needed to determine whether new vector control products that enter an established class should be assessed for similar or better performance compared to the first-in-class product. If so, what methodology should be used for this purpose?

4. To advise WHO on the data requirements and methodology needed to assess products with two active ingredients and the process to establish a new product class.

4. Review of SumiShield® 50WG

Summary of WHOPES experimental hut and large-scale community trials to evaluate efficacy

SumiShield® 50WG is an IRS product containing clothianidin 50.0% (w/w). This is a neonicotinoid-based IRS formulation that contains a new chemical active ingredient (AI) compared to existing IRS products with a WHO policy recommendation. In its assessment of SumiShield® 50WG, the ERG reviewed data from trials conducted in four countries following the WHO Pesticide Evaluation Scheme (WHOPES) guidelines for testing IRS products. The most comprehensive assessment was based on data from laboratory studies (WHOPES Phase 1) (Box 1), field trials conducted in the United Republic of Tanzania (Box 2), and supported by preliminary assessment of the results from trials in three other countries (Box 3).

Box 1. Summary of residual efficacy test

Test parameters – laboratory evaluation (WHOPES Phase I)

Following studies were conducted:

- Intrinsic toxicity of clothianidin AI by topical application on susceptible, pyrethroid resistant (kdr) and organophosphate/carbamate resistant (Ace1R) strains of *An. gambiae*;
- Cross-resistance test: Comparing 1) the KD and mortality induced by clothianidin and deltamethrin AIs, at the discriminating concentrations, against pyrethroid-resistant mosquitoes; 2) mortality induced by clothianidin and propoxur at the discriminating concentrations, against organophosphate/carbamate resistant strain;
- Efficacy and residual activity evaluation of SumiShield® 50WG in cone tests on different substrates (cement, mud and wood) against susceptible *An. gambiae* at the dosage of 200 mg AI/m² and 300 mg AI/m², with 30 minutes exposure; 60 minutes post-exposure KD; and scoring mortality at 0, 1, 2, 3, 4, 6, 8, 10 and 13 months after treatment of substrates.
Summary of findings:

- SumiShield® 50WG demonstrated a residual activity (≥ 80% mortality) of more than 12 months on wood and cement substrates with 200 mg AI/m² and 300 mg AI/m² dosage. The highest dosage (300 mg AI/m²) also gave a residual activity for 10 months on mud substrate when considering the mosquito mortality at 72 hours post exposure. The dose of 300 mg/m² should be applied in the context of traditional houses where walls are mainly made up of mud.

- Using topical application, no cross-resistance to pyrethroid, organophosphate and carbamate insecticides was observed for resistant Anopheles strains having target site mutations on voltage dependent sodium channels (kdr mutation L1014F) or acetylcholinesterase (Ace-1R, G119S).

Box 2. Summary of trials to evaluate SumiShield® 50WG for IRS in the United Republic of Tanzania

Experimental hut – small-scale field trials (WHOPES Phase II)

**Design:** Single-blinded, partially randomized, Latin square evaluation with five treatment arms (four IRS products, one negative control) in 10 huts; allocation of treatment by lottery method; investigators/participants blinded; 8 months of follow-up observations

**Outcomes:** Immediate and delayed vector mortality, blood feeding inhibition, insecticide residual activity, deterrence and induced exophily, as well as infectivity (sporozoite) rate and Entomological inoculation rate (EIR)

**Summary of findings**

- Local wild An. arabiensis was resistant to pyrethroids and susceptible to all other classes of insecticides (organophosphate – pirimiphos methyl, fenitrothion and malathion; carbamate – bendiocarb; and organochlorine – DDT); local wild An. funestus was resistant to pyrethroids and organochlorine DDT, partially resistant to carbamate (bendiocarb), and susceptible to organophosphate (pirimiphos methyl, fenitrothion and malathion) and organochlorine (dieldrin).

- Mortality induced by SumiShield® 50WG in cone bioassay tests on sprayed walls against pyrethroid-susceptible An. gambiae s.s. was less than 80% after 30-minute exposure at 24-hour holding time; the same was observed for comparator products (K-Othrine® 250WG, Actellic® 300CS and Ficam® 80WP). Mortality induced by SumiShield® 50WG increased substantially with a prolonged holding time of 72 hours.

- SumiShield® 50WG showed greater mortality in the mosquito vector than the three comparator insecticides (pyrethroid, carbamate and organophosphate), against wild An. arabiensis at 24-hour holding time.

- SumiShield® 50WG continued to kill a greater proportion of wild An. arabiensis than the three comparator insecticides up to 8 months after spray application using a 24-hour holding time.
• SumiShield® 50WG demonstrated increasing toxicity to *An. arabiensis* at holding times beyond 24 hours and at each holding time killed a greater proportion of *An. arabiensis* than the other three insecticides.

*Community study – Large-scale field trials (WHOPES Phase III)*

**Design:** Single-blinded, two IRS treatment arms with five clusters per arm, around 200 households/cluster with clusters 2 km apart; treatment arms: SumiShield® 50WG and Actellic® 300CS

**Outcomes:** Residual and biological efficacy of insecticide, insecticide susceptibility of target vector species, vector density, vector longevity, vector mortality, infectivity rate (sporozoite rate)

**Summary of findings**

• Primary vector *An. funestus* and secondary vector *An. arabiensis* were resistant to all types of pyrethroids and susceptible to organophosphate- pyrimiphos-methyl.

• Performance of SumiShield® 50WG applied at 300 mg Al/m² was equal or superior to the reference product Actellic® 300CS applied at 1 g Al/m² for each of the outcomes measured.

• The residual efficacy (≥80% vector mortality in cone bioassay) of SumiShield® 50WG and Actellic® 300CS applied to baked brick houses against pyrethroid-susceptible *An. gambiae s.s.* was:
  - 3 months measured at a 24-hour holding time for both products;
  - 7 months for SumiShield® 50WG and 4 months for Actellic® 300CS at a 72-hour holding time.

• The mortality of wild mosquitoes was greater in the SumiShield® 50WG arm than in the Actellic® 300CS arm for both the *An. arabiensis* and *An. funestus* vector species in the area.

• There was no statistical difference between the infectivity rates of the two treatment arms for both vector species.

• There was no statistical difference in the density of vectors (*An. arabiensis* & *An. funestus*), infectivity (sporozoite) rates and EIRs between the SumiShield® 50WG and Actellic® 300CS arms.

**Overall conclusions**

Over 8 months in experimental huts, SumiShield® 50WG showed superior efficacy to the other three IRS products based on 24-hour vector mortality. SumiShield® 50WG demonstrated a duration of efficacy comparable to that of Actellic® 300CS, i.e., 3 months at 24-hour holding and 7 months at 72-hour holding time in the community randomized trial. SumiShield® 50WG was effective at the current standard 24-hour mortality cut-off criteria. This result would have satisfied the efficacy criteria under the former WHOPES evaluation process. Data from the cluster randomized trial were insufficient to measure non-inferiority, but this was not required under the former WHOPES process.
Box 3. Summary of trials to evaluate SumiShield® 50WG in Benin, Côte d'Ivoire and India

The ERG assessed findings based on trials conducted in Benin (two studies Phase II: in Cové and Malanville), Côte d'Ivoire (one each Phase II and III) and India (one each Phase II and III). This assessment by the ERG is preliminary because it is based on a rapid review of the available data. The ERG made the following observations:

- SumiShield® 50WG induced a mortality of >80% (24-hour holding time) on a fully susceptible vector strain in bioassays for up to 3 months of IRS in Benin (Cové) and India, 4 months in Benin (Malanville) and 6 months in Côte d'Ivoire. Mortality increased substantially for fully susceptible and resistant strains of vectors with a prolonged holding time of 72 hours.

- Slow killing effect of SumiShield® 50WG (clothianidin at 300 mg AI/m²) was also seen against both susceptible and resistant Anopheles populations. Comparator products also showed increased delayed mortality but to a lesser degree than with SumiShield® 50WG.

- Efficacy of SumiShield® 50WG was beyond 6 months.

- The effect of clothianidin on fertility (i.e., number of eggs and viability of embryos) is unknown.

A detailed review and critical analysis of data from these studies (conducted in Benin, Côte d'Ivoire and India) is necessary in order to add to the evidence base on the efficacy of SumiShield® 50WG.

Specific discussion on SumiShield® 50WG based on data reviewed

Current efficacy criteria require an IRS product to demonstrate at least 80% mortality of insecticide-susceptible anopheline mosquitoes held in a cone bioassay for 24 hours after exposure to insecticide applied to the most common wall substrates. This mortality effect needs to continue for at least 3 months after the application of the insecticide to the substrate, usually cement, mud and wood. Besides cone bioassay studies, cross-resistance studies in laboratory settings against mosquito strains with different resistance mechanisms should also be conducted, and the killing effect and blood feeding inhibition effect on wild vector populations in experimental huts should be assessed in comparison to a positive control (3).

The mortality of fully susceptible mosquitoes exposed in a cone bioassay to walls treated with a target dose of 300 mg AI/m² of SumiShield® 50WG was equal to or greater than 80% at 24 hours for most studies, and at 72 hours for all studies, for 4–8 months. The evidence also showed improved performance for extended holding times post-exposure in cone bioassays, indicating improved efficacy with longer exposures. Based on data from the studies in the United Republic of Tanzania, which compared SumiShield® 50WG to the pyrethroid deltamethrin (K-Othrine® 250WG at 25 mg Al/m²), the organophosphate primiphos methyl (Actellic® 300CS at 1 g Al/m²) and the carbamate bendiocarb (Ficam® 80WP at 400 mg Al/m²), SumiShield® 50WG was found to perform as well as or better than these comparator products. On the basis of these findings, and with the results of additional small-scale and community entomological trials, SumiShield® 50WG would meet the current WHOPES efficacy criteria for IRS products.
Under the former WHOPES process, SumiShield® 50WG would have been recommended for deployment on the basis of the evidence reviewed by this ERG. Considerations surrounding deployment guidance should be discussed by another group, particularly to address the utility of this product for insecticide resistance management.

SumiShield® 50WG has only been assessed for efficacy as an IRS product, not against a claim of being effective in controlling insecticide-resistant mosquitoes. SumiShield® 50WG is the first neonicotinoid-based IRS product. Potentially, this product may provide an alternative for use in insecticide rotation as a strategy to manage insecticide resistance in vector control programmes. Neonicotinoid-based products are widely used in agriculture; this has caused selection pressure leading to the development of resistance, as demonstrated by widespread metabolic resistance in crop pests due to enhanced cytochrome P450 activity (4). Based on the data reviewed, cross-resistance against SumiShield® 50WG cannot be excluded. First, the mortality induced by SumiShield® 50WG on wild mosquitoes was around 30% for up to a 168-hour holding time after 30-minute exposure. Second, mortality rates in cone bioassays for a 24-hour holding time were higher against the susceptible strain than against the pyrethroid-resistant strain tested.

Data reviewed also indicate that SumiShield® 50WG’s efficacy is at a >80% mortality threshold for a 72-hour holding time. This should be considered in the assessment of the product. In the future evaluation of IRS products, data from 30-minute exposures in cone bioassays with both 24-hour and 72-hour holding times should be used to assess delayed effects on target vectors.

**General discussion on the evaluation of IRS products**

Given the limited epidemiological data for IRS linking entomological surrogates to epidemiological impact, the current standard is to rely on data from experimental hut studies with a study design that is properly powered and randomized with adequate replication. At present, evidence that entomological effects determined in laboratory or small-scale field studies predict epidemiological outcomes determined in cluster randomized trials (CRTs) is scant, mainly due to the limited number of CRTs conducted. The relationship between experimental hut trials and CRTs can be explored in multiple ways. For example, experimental hut trials can be conducted in the vicinity of CRTs in order to assess entomological outcomes in relation to the spatial heterogeneity in vector species (composition, behaviour and insecticide resistance).

This ERG sees the value of large-scale effectiveness (Phase IV) studies to verify the relevance of current entomological measurements for predicting epidemiological impact. Also, the group encourages multiple comparisons across different IRS products of different chemical classes in experimental hut studies in order to identify the appropriate comparators for community randomized trials (WHOPES Phase III) or epidemiological CRTs with disease endpoints. Data based on multiple comparators are also useful for informing the rotation of active ingredients for resistance management.

Future IRS products will include new AIs with novel mechanisms of action. New AIs such as chlorfenapyr, which targets cellular and mitochondrial respiration under circadian rhythm control, may not reach 80% mortality after 30-minute exposure in cone bioassays under daytime conditions. Innovators are encouraged to think ‘outside the box’ and not feel tied to cone mortality thresholds, as these seem to be better criteria for the neuro-acting AIs of the IRS products commonly used in public health.
Key conclusions on SumiShield® 50WG

The ERG made the following observations based on the results of experimental hut and long-term community trials from four sites (United Republic of Tanzania, India, Côte d’Ivoire and Benin).

1. SumiShield® 50WG satisfies the current criteria for efficacy according to the WHOPES guidelines for testing the efficacy of IRS products. This observation is based on the review of data on the mortality of fully susceptible mosquitoes exposed to substrates and walls treated with a target dose of 300 mg AI/m². Percentage mortality in cone bioassays after 30-minute exposure at a 24-hour holding time was equal to or greater than 80% for most studies and exceeded this threshold after a 72-hour holding period in all studies for a duration of 4–8 months following the application of the insecticide.

2. SumiShield® 50WG also showed improved performance for extended holding times post-exposure, indicating improved efficacy with longer exposure. A similar trend was seen with all comparator IRS products, which included pyrethroid-, carbamate- and organophosphate-based IRS formulations recommended by WHO.

3. Novel SumiShield® 50WG product claims will need to be defined and assessed with the support of WHO.

5. Review of pyrethroid-PBO nets

Current status

Five pyrethroid-PBO net products were evaluated under WHOPES to determine whether they met the criteria established for classification as a pyrethroid-treated long-lasting insecticidal net (LLIN) (5). The WHOPES Phase I and II evaluation assessed the biological activity and wash resistance of the pyrethroid treatment and the PBO component. Given that no manufacturer of submitted products claimed that PBO provided added efficacy against pyrethroid-resistant mosquitoes, the WHOPES recommendations for pyrethroid-PBO nets are based on an evaluation of the efficacy of the nets’ pyrethroid components against susceptible mosquitoes.

Of the five pyrethroid-PBO nets evaluated by WHOPES, all underwent experimental hut evaluations, and two are currently undergoing long-term field evaluations (WHOPES Phase III) with entomological endpoints. A cluster randomized controlled trial (CRCT) in the United Republic of Tanzania has generated new epidemiological evidence for pyrethroid-PBO nets. Results of the first 2 years of the Tanzanian trial were reviewed by the WHO ERG on pyrethroid-PBO nets held in June 2017 in order to assess whether the new data demonstrated the public health value of pyrethroid-PBO nets in terms of the control of malaria where vectors are pyrethroid-resistant. Based on this review, the recommendations on the conditions for deployment of pyrethroid-PBO nets have been updated (6).

The ongoing trial in the United Republic of Tanzania will provide 3rd-year data on durability and the effect of pyrethroid-PBO nets on disease outcomes, thus generating evidence on the long-term efficacy of pyrethroid-PBO nets. A second randomized controlled trial is planned in Uganda; this trial will include two pyrethroid-PBO nets (one with PBO in all panels and another with PBO on the roof alone). Results will provide further data on the
performance of two main types of pyrethroid-PBO nets and inform choices for appropriate future comparators for this new product class.

Available data on the efficacy of pyrethroid-PBO nets against pyrethroid resistance do not cover all known resistance mechanisms. It is necessary, therefore, to assess the efficacy of such products against strains that represent all types of resistance mechanisms, particularly oxidase-mediated resistance.

Assessment of PBO retention and bioavailability

In order to meet the current WHO criteria for an LLIN, the pyrethroid content in a pyrethroid-PBO net must withstand at least 20 standard washes in laboratory and 3 years of field performance (efficacy). Both chemical and physical durability are critical in terms of an LLIN’s effectiveness. The synergistic effect of PBO on pyrethroid can only be maintained if the PBO is biologically available on the surface of the netting fibres. In order to maintain the efficacy of a pyrethroid-PBO net, ideally both the pyrethroid and PBO components need to remain biologically available for at least 20 laboratory washes and throughout the expected life of the net in field (at least 3 years), in which case it can qualify as a pyrethroid-PBO LLIN (long-lasting for both the AI and the synergist).

WHOPES wash-resistance testing is currently used to assess the nets’ retention of the chemical content (AI and PBO) during the wash procedure. The amount of AI/PBO lost in each consecutive wash is taken as the chemical content that was available on the net’s surface prior to washing. Currently, there is no other chemical method to determine the surface content of the AI or PBO. Therefore, the bioavailability of this surface content is determined in a proxy way through cone bioassays using susceptible mosquitoes after different wash points (e.g., 0, 1, 3, 5, 10, 15, 20 or more washes).

A broad review of WHOPES trial outcomes indicates that for pyrethroid-PBO nets, PBO retention after 20 washes in laboratory studies (Phase I) and experimental hut studies (Phase II) is for the most part lower than pyrethroid retention on those same nets. This discrepancy is probably due to the fact that since PBO is lipophilic, repeated washes with soap remove the PBO content. However, the curve of the retention rate according to the number of washes is more informative than the average retention rate. When there is no decline in PBO content between consecutive washes (e.g., between 5, 10, 15 and 20 washes), it implies that PBO is no longer being released from the inner core of the net fibres onto the surface. In the field, however, in addition to washing, aging and environmental factors may also contribute to accelerated or greater reductions in AI and PBO as the nets degrade over time. Further data are needed to understand whether current washing procedures reliably correlate with the degradation of AIs and synergists in the field.

The PBO retention after 1 and 2 years of household use of the nets in a large-scale community trial (Phase III) has been found to be still lower than the retention with wash procedures in Phase I and II studies. This suggests that, in addition to a higher release rate of PBO, some chemical degradation of PBO may occur over time due to environmental factors and local wash practices. Epidemiological data from one CRCT conducted in the United Republic of Tanzania suggest that pyrethroid-PBO nets may have additional public health value (6). However, no clear pattern was observed between the PBO content of a range of different pyrethroid-PBO nets assessed in WHOPES Phase I and II trials and their measured entomological efficacy. This suggests that total PBO retention alone is not
sufficient to estimate the efficacy of pyrethroid-PBO nets; bioavailability data against susceptible and resistant species should be investigated during field use of the nets.

To date, there are insufficient data to define the relationship between PBO content and its biological efficacy against resistant mosquitoes over time. Based on the data reviewed, the ERG was not able to define what number of washes is essential for PBO availability and its duration of synergist effect with pyrethroid AI on the net to define it as a PBO LLIN. This question needs to be reviewed when more field data become available. New criteria will likely be required to assess the persistence and bioavailability of PBO over time. Such criteria include the amount of PBO retained in the net fabric, released and bioavailable on the surface of the net fibres. Obtaining these data will involve the further development of chemical and bioassay methods for all assessments.

Entomological surrogate for disease impact

Experimental hut trials are designed to assess the entomological efficacy of nets and to assess the durability (wear and tear) of nets under field conditions. These aspects are then subsequently tested in Phase III field trials either using entomological outcomes alone or including epidemiological outcomes. At present, it is unclear as to whether entomological efficacy estimates obtained from experimental hut trials are sufficient to evaluate either the entomological or the epidemiological impact of LLINs or PBO-LLINs, and in particular whether they are sufficient to establish non-inferiority² to existing LLINs.

To improve our understanding of the entomological correlates of disease outcomes, it would be beneficial to conduct hut trials and large-scale CRTs (with disease endpoints) at the same site. Furthermore, conducting experimental hut trials to re-test LLINs that were previously tested in WHOPES Phase III trials with disease outcomes (or in CRCTs such as the Tanzanian trial) may be helpful to establish entomological surrogates of efficacy. While current proxies for the impact of new LLINs are based on experimental hut data, there remains a concern that experimental huts may not capture the efficacy of LLINs or pyrethroid-PBO nets in real-life situations. This may result in an underestimation or overestimation of mortality counts due to the impact of hut size on vector behaviour, which may affect, for example, the likelihood that a vector rests on the top (PBO-containing) panel of a net. A full-sized hut may therefore be better for estimating variations in pyrethroid-PBO location.

Until new data are available for review, current experimental hut procedures, as described in the WHO guidelines for testing LLIN products, should be followed for new LLIN products with PBO synergists. Furthermore, it is important to emphasize that the evaluation of vector control products such as LLINs must be based on robust and well-implemented study designs. The ERG therefore recommends that WHO convene a group of experts to provide guidance on the design, execution and reporting of experimental hut studies.

² A vector product under evaluation shows non-inferiority when it demonstrates an equal or better entomological effect and/or protective efficacy against infection and/or disease in humans in reference to a comparator product. Non-inferiority relies on a measurement of effect whereby the difference should be only a small amount, called the non-inferiority margin, or delta. Delta is pre-specified based on the desired clinical (or entomological) effect. Specifying a smaller delta for a non-inferiority trial can test whether a new product’s performance is similar to that of a comparator product (i.e., difference of effects is <delta), but demonstrating statistical significance may require larger sample sizes.
Choice of comparator net to evaluate new and existing pyrethroid-PBO nets

Given the diversity of nets in relation to where the PBO is located (e.g., on the net as a whole or on the roof panel only), it is not clear what kind of comparator product should be chosen for subsequent in-class products. Data from the CRCT in the United Republic of Tanzania have demonstrated the epidemiological impact of pyrethroid-PBO nets with PBO on all panels (5). This product therefore represents the “first-in-class” for the new product class.

Ongoing community randomized trials involving variations in PBO nets (i.e., PBO in all panels vs. PBO on the roof alone) will provide more evidence to enable broad recommendations on PBO nets and the choice of comparator for subsequent evaluations. Until more data are available, the evaluation of nets with PBO should, at minimum, include a single comparator that represents the standard of care where the trial is implemented.

In order to encourage innovation, future investigations should consider multiple comparators with different types of pyrethroid-PBO nets and LLINs with new AIs, as well as standard pyrethroid-PBO nets, in order to assess differential effectiveness among various types of LLINs.

Key conclusions specific to pyrethroid-PBO nets

1) The current definition of a long-lasting net applies to the pyrethroid components in LLINs, which must withstand 20 washes in laboratory and 3 years efficacy in the field in order to qualify under the pyrethroid-LLIN product class. There is currently insufficient evidence to define the required durability of the PBO component; this will need to be reviewed as more data become available.

2) Evaluation of nets with PBO should, at minimum, include a single comparator that represents the standard of care where the trial is implemented. Multiple comparisons between pyrethroid-PBO nets (variants) are encouraged to inform implementation.

3) The relationship between entomological efficacy in experimental hut studies and entomological and epidemiological efficacy in CRTs should be further explored to assess whether experimental hut studies can be used in the future to assess the non-inferiority of new net products.

6. Larvicide products

Specific discussion on the Larvasonic SD-Mini device

The Larvasonic SD-Mini is a device that emits underwater sound pulses that cause rapid larval death by rupturing larval dorsal tracheal trunks. The intervention is a larvicidal device that is placed in containers or bodies of water, and as such can be used to target mosquitoes breeding in urban containers. The manufacturer of the product claims that it will be effective against all species at all aquatic stages (larvae and pupae), that it does not affect non-target organisms, and that it will not induce insecticide resistance.

VCAG reviewed the first prototype, Acoustic Larvicide™, in 2014. Acoustic larvicides, like chemical larvicides, kill larvae and thus require that each larval habitat be located and treated. Based on the evidence presented, VCAG concluded that this product falls under an
established class of larvicides that includes insecticide-based, juvenile hormone mimics and biological actives (e.g., Bti). Given the novelty in the mode of action of this mechanical larvicide and its potential utility in public health vector control, particularly for dengue-endemic regions, VCAG concluded that this tool could be evaluated using the WHOPES guidelines for laboratory and field testing of mosquito larvicides. The ERG concurs with VCAG’s conclusions and recommends that evaluations of the Larvasonic SD-Mini device follow existing WHOPES guidelines, including a safety validation and risk assessment of acoustic sound on non-target organisms. The comparator should be a classic larvicide product with a WHOPES recommendation. Subsequent evaluation of a second-in-line sonic device should ideally be evaluated against a first-in-class sonic device in addition to a classic larvicide.

General discussion on larvicides

Currently, WHO recommends larviciding for malaria control as a supplement to LLINs or IRS, only in areas where the anopheline larval habitats are few, fixed and findable (8). Larviciding is widely used to treat Ae. aegypti larval habitats and should be considered a complement to environmental management — except in emergencies — and restricted to containers in which larvae cannot be otherwise eliminated or managed. Currently, one CRT being conducted at sites in Nicaragua and Mexico, with community participation in larval source reduction measures, has shown the impact of larvicide in reducing the number of dengue cases (9).

Generally, however, there have been few studies on the effects of larvicides/larvicidal devices on disease endpoints (10). Such evidence should be generated and systematically reviewed to support the use of these interventions for public health purposes.

Key conclusions on larvicides

1) Current WHO guidelines on testing larvicides will apply to this mechanical larvicide device, Larvasonic SD-Mini.

2) The ERG recommends that WHO review the policies on larval source management intervention types in order to guide the generation of the required additional evidence with which to determine their public health value.

7. Space spray products

Specific discussion on Fludora® Co-Max EW

This is the first space spray product with a mixture of two AIs: flupyradifurone (a neonicotinoid) and transfluthrin (pyrethroid). The efficacy of both AIs can be measured using the same efficacy endpoints currently specified by WHO. This product complies with a category of space spray class covered by the current WHO policy and, as such, should be evaluated following the WHOPES guidelines for the efficacy testing of insecticides for indoor and outdoor ground-applied space spray applications (11).

The rationale for a mixture space spray with more than one AI from different insecticide classes is based on the claim that both AIs intend to kill; hence, having more than one AI should reduce the emergence or spread of resistance. High-dose, short-lived AIs are most
appropriate for managing resistance, because it is unlikely that such situations will lead to enhanced selection pressure for resistance.

This being the first space spray product with a mixture of two AIs from different insecticide classes, it may be necessary to include an additional efficacy claim. If the product claims efficacy against resistant mosquitoes, this will need to be demonstrated. This may require additional guidance from WHO on how to demonstrate such claims and a revision of existing WHO test procedures.

Space spray evaluations can be done through indoor and/or outdoor applications that involve scoring the mortality of susceptible mosquitoes in control cages. The current test procedure does not require the assessment of the efficacy of the product against wild mosquitoes in test cages. While current test guidelines outline procedures to be used for operational field trials for assessing the product’s efficacy against wild mosquito populations, due to the practicality of implementing such trials, they are not currently part of the efficacy evaluation. In order to improve the feasibility of such evaluation and ensure robust assessment, expert advice on study design and sample size calculation is needed. Alternative trial designs should be considered, such as a stepped-wedge design, to allow for adequate replication.

In general, there is a lack of evidence on the impact of space spraying on disease outcomes for diseases such as malaria and dengue. The aim of space spraying is to cause massive killing with frequent spray cycles, leading to a rapid reduction of the adult vector population. Any control method that reduces the number of infective adult mosquitoes, even for a short time, should reduce parasite or virus transmission during that time; however, it remains unclear as to whether the impact of space treatments is epidemiologically significant. Factors such as the insecticide susceptibility of the target vector, droplet size in space sprays, application rate, and frequency of spraying and indoor penetration of the insecticide droplets are all crucial to the efficacy of this method.

Currently, space spraying is recommended for control only in emergency situations to suppress an ongoing dengue/arboviral disease epidemic or to prevent an incipient one. A recent review concluded that indoor space spraying is an effective adulticidal intervention against Aedes mosquitoes (12). As the current policy recommendations for space spraying are based on historical data and grey literature, there is a need to generate strong evidence on the impact of space spraying on wild mosquito populations and to assess the impact on disease in order to determine whether the intervention has public health value.

**Key conclusions**

1) The ERG recognizes that there is a lack of evidence on the impact of space spraying on disease endpoints. This body of evidence should be generated in order to support the use of space sprays for public health.

2) The group recommends that WHO conduct a review of the policies for space spraying in order to guide the generation of the additional evidence required to determine the intervention’s public health value.
Annex 1. Agenda

General objectives
1. To advise WHO on the data requirements and methodology needed to determine whether the existing WHO policy for a class of products can be extended to recommend the deployment of a new vector control intervention that is not part of the class, but for which entomological effects are sufficiently similar to consider an extension of the policy.

2. To apply criteria formulated under objective 1 to the assessment of SumiShield® 50WG, and to advise WHO on whether current policy recommendations for IRS products should be extended to this new insecticide and, if so, whether there should be conditions associated with the extension of the policy.

3. To advise WHO on the data requirements and methodology needed to determine whether new vector control products that enter an established class should be assessed for similar or better performance than the first-in-class product. If so, what methodology should be used for this purpose?

4. To advise WHO on the data requirements and methodology needed to assess products with two active ingredients and the process required to establish a new product class.

Specific questions to be addressed under each of these objectives are outlined in the ERG’s Terms of Reference.

Provisional programme

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<td>09.00 – 09.15 Registration</td>
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<tr>
<td>09.15 – 09.45 Opening remarks and welcome Dr Pedro Alonso</td>
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<td>09.45 – 09.50 Declaration of interest Dr Pedro Alonso</td>
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<tr>
<td>09.50 – 10.00 Background, objectives and expected outcomes Dr Emmanuel Temu</td>
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<td>10.00 – 10.30 Coffee break</td>
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**Part I: Data and methodology to inform potential extension of existing policy recommendations to new interventions**

<table>
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<tr>
<td>10.30 – 10.45 Overview of the revised WHO evaluation process for vector control products Dr Raman Velayudhan</td>
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<tr>
<td>10.45 – 11.00 SumiShield® 50WG Phase 1 Data and WHOPES evaluation Dr Rajpal Yadav</td>
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<tr>
<td>11.00 – 11.30 SumiShield® 50WG for IRS (India and Cote d’Ivoire data) Dr Marc Coosemans</td>
</tr>
<tr>
<td>11.30 – 12.00 SumiShield® 50WG for IRS (Tanzania Data) Dr Sarah Moore</td>
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<tr>
<td>Time</td>
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<td>12.00 – 12.30</td>
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**Wednesday 13 September 2017**

**Open Session**

**Part II: Presentation of current evidence on a selection of new vector control tools & determination of the data and methods required to comparative effectiveness**

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<tr>
<td>09.00 – 9.45</td>
<td>Brief introduction to WHOPES evaluation of LLINs/nets</td>
<td>Dr Rajpal Yadav</td>
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<tr>
<td>09.45 – 10.00</td>
<td>PBO nets with WHOPES recommendation</td>
<td>Dr Rajpal Yadav</td>
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<tr>
<td>10.00 – 10.30</td>
<td>Discussion &amp; determination of criteria required to include other pyrethroid + PBO nets into the class established by Olyset Duo</td>
<td>Chair</td>
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<td>10.30 – 11.00</td>
<td>Coffee break</td>
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<tr>
<td>11.00 – 11.15</td>
<td>Brief introduction to WHOPES evaluation of larvicides</td>
<td>Dr Anna Drexler</td>
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<tr>
<td>11.15 – 11.45</td>
<td>Larvicidal products (Larvasonic SD-Mini device)</td>
<td>Dr Anna Drexler</td>
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<tr>
<td>11.45 – 12.30</td>
<td>Discussion &amp; determination of how new larvicides and larvicidal devices should be assessed to inform extension of policy</td>
<td>Chair</td>
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<tr>
<td>12.30 – 13.30</td>
<td>Lunch</td>
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<tr>
<td>13.30 – 13.45</td>
<td>Brief introduction to WHOPES evaluation of space sprays</td>
<td>Dr Raman Velayudhan</td>
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<td>13.45 – 14.15</td>
<td>Space sprays (Fludora® Co-Max EW)</td>
<td>Dr Velayudhan /Amy Morrison</td>
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<tr>
<td>14.15 – 15.00</td>
<td>Discussion &amp; determination of how space sprays should be assessed to inform extension of policy</td>
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<td>15.30 – 17.00</td>
<td>Discussion on data requirements and methodological issues identified during day 2</td>
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<td>17.00 – 17.30</td>
<td>Summary of decisions reached on Day 2</td>
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### Thursday 14 September 2017

Closed Session

#### Part III: Formulation of draft recommendations

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<tr>
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<tr>
<td>09.00 – 10.30</td>
<td>Drafting of recommendations on the assessment of new tools that do not fall within an established class but for which entomological effects seems sufficiently similar to consider extension of policy (and hence avoid epidemiological studies prior to deployment)</td>
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<tr>
<td>10.30 - 11.00</td>
<td>Coffee break</td>
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<tr>
<td>11.00 - 13.00</td>
<td>Drafting of recommendations on the assessment of products falling within an established class. Does such assessment need to inform whether they perform as well as, or better than, the first-in-class product (or another suitable comparator)?</td>
<td>Chair</td>
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<tr>
<td>13.00 - 14.00</td>
<td>Lunch</td>
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<td>14.00 - 15.30</td>
<td>Final discussions and next steps</td>
<td>Chair</td>
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<tr>
<td>15.30 – 15.45</td>
<td>Meeting closure</td>
<td>Dr Pedro Alonso</td>
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Annex 2 – LIST OF PARTICIPANTS

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References


