Preferred product characteristics: indoor residual spraying products for malaria transmission control in areas with insecticide-resistant mosquito populations
Draft for public consultation

Overview
The Global technical strategy for malaria 2016–2030 (GTS) aims to harness and expand research to accelerate progress towards the elimination of malaria and to counteract the emerging threat of drug and insecticide resistance (1). It encourages innovation and the development of new tools, technologies and strategies (collectively referred to as ‘interventions’) to maintain progress in malaria control and to further advance towards elimination. To accelerate implementation of the GTS, the World Health Organization’s (WHO) Global Malaria Programme (GMP) conducted a review of its guidelines and guidance development processes, to ensure transparency, consistency, efficiency, and predictability. One of the outcomes of the review was the adoption of “preferred product characteristics” (PPCs) to incentivize and guide the development of urgently needed health products. The use of PPCs is aligned with an organization-wide effort to improve WHO’s communication on identified public health needs and to encourage and facilitate innovation to meet those needs.

WHO PPCs aim to:

- communicate unmet public health needs;
- stimulate the development of relevant new products to meet those needs; and
- facilitate the timely, effective assessment of new products, and the formulation of WHO recommendations and prequalification listings.

Within GMP, the Vector Control & Insecticide Resistance Unit is developing a series of PPCs to encourage further innovation in vector control. The PPC published here describes the characteristics of new products for indoor residual spraying (IRS) designed to control malaria transmission in areas with insecticide-resistant mosquito populations. The document was developed to address the public health need caused by the evolution and spread of insecticide resistance. Insecticide resistance is one of the identified threats to the effectiveness of the current interventions for malaria vector control, including IRS (1).

Terminology
Preferred product characteristics (PPCs) are designed to communicate unmet public health needs identified by WHO, stimulate innovation and investment in the identified areas, and communicate the desired performance and operational characteristics of health products to address those needs. The target audience consists of product developers, regulatory agencies, procurement agencies, and funders.

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of research and development and public health priorities. PPCs accommodate a number of target product profiles (TPPs).

**Target product profiles (TPPs)** are planning tools used by manufacturers to guide the development of specific products. TPPs generally provide much more detailed information than PPCs, such as intended use, target populations, and safety and efficacy-related characteristics. They include both minimally acceptable and preferred performance characteristics. The minimum performance characteristics should be considered a “go/no-go” decision point in the product development process. The preferred product characteristics should reflect the ideal characteristics required to rapidly and effectively achieve a global health impact.

**Indoor residual spraying (IRS) products for malaria transmission control in areas with insecticide-resistant mosquito populations**

**Background and purpose**

IRS is one of two malaria vector control interventions currently recommended by WHO for large-scale deployment, the other being insecticide-treated nets (ITNs) (2). WHO’s recommendation for IRS is based largely on historical and programme information; a systematic review of the evidence on the disease-control impact of this intervention was unable to quantify the effect size of this intervention in different transmission settings and encouraged further trials to strengthen the evidence-base (3). Five classes of insecticides are currently covered by the recommendation, namely carbamates, neonicotinoids, organophosphates, pyrethroids and, as an option of last resort, the organochlorine DDT, provided it is used in full compliance with the Stockholm Convention on Persistent Pollutants. WHO prequalified IRS products are available for these insecticide classes, except for DDT. No manufacturer has submitted an application to WHO requesting assessment of a DDT IRS product for the purpose of prequalification.

IRS is one of a number of potential intervention classes under the overarching intervention type of ‘residual insecticide surface treatment’ (4). While the term ‘IRS’ is being retained for historical reasons, the WHO categorization of existing and potential new vector control interventions has been evolved to refer to this intervention as ‘Full indoor surface fast-acting formulations’. Conceptually this intervention class therefore also covers insecticidal paints, although no products have been prequalified in this category to date. The establishment of other intervention classes under the umbrella of ‘residual insecticide surface treatment’ is anticipated, based on the evaluation of ‘first-in-class’ products, with potential classes covering categories such as products that are slower-acting than products currently covered by the WHO recommendation, use patterns that targets only parts of indoor walls, or the use of insecticide-treated materials, such as wallpaper. While the term ‘insecticide’ is used to describe the intervention type and some of the provisional classes, this terminology should not limit innovation in this field. The entomological effect(s) achieved by IRS as it is currently used may be achieved by treating/covering indoor walls with products other than those containing conventional insecticides. The classification may therefore need to be evolved; its purpose is not to inform innovation in this space but to indicate how products presently identified through horizon scanning would need to be evaluated to inform WHO recommendations and associated prequalification listings (4).

This PPC was developed to stimulate further innovation in this area by outline the identified public health need for new IRS products and of the preferred products characteristics to address this need. The public health need has arisen due to the evolution and spread of resistance in mosquito vectors to most of the insecticide classes currently used for IRS. Insecticide resistance now poses a significant threat to the
continued effectiveness of this and other insecticide-based interventions for malaria vector control (5). Development of new vector control interventions, including IRS products designed to be effective against mosquito populations resistant to insecticides, is thus essential to provide options for insecticide resistance management and to contribute to meeting the milestones of the GTS (1).

The characteristics outlined below reflect, to a certain extent, those of current IRS products, because the intervention approach – namely applying a substance to the indoor walls of a permanent structure – remains the same. Given ongoing and anticipated developments in this area, this PPC document will be dynamic and will be updated as new information indicate the need to make changes to the parameters and characteristics and/or to the identified public health need itself.

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<th>Preferred product characteristic</th>
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| Indication | • Uses any mechanism expected to reduce vectorial capacity so as to provide community protection to individuals.  
• Prevention of biting (human-vector contact) is considered an added advantage.  
• Reduces or prevents infection and/or disease caused by malaria in humans.  
• Suitable for use on a variety of substrates used to construct and cover interior walls and other house structures. |
| Target population – human | • Populations at risk of malaria |
| Target population – disease vector | • *Anopheles* mosquitoes, including strains resistant to insecticides in current use (pyrethroids, organophosphates, carbamates, neonicotinoids and organochlorines). Resistance mechanisms to be overcome include: target-site (Kdr, AChE, RDL, nAChR) and metabolic (monooxygenases, esterases, glutathione S-transferases). The current priority is for products that effectively control pyrethroid- and/or organophosphate resistant mosquito populations.  
• Control of other arthropod vectors and/or nuisance-biting arthropods is considered an added advantage. |
<p>| Epidemiological efficacy | • Protective efficacy to reduce and/or prevent malaria infection and/or disease in humans in areas where the primary vector(s) is/are resistant to insecticides. Efficacy should be equivalent to that of currently available IRS products when used in areas where the vector(s) is/are susceptible to the product being used. Alternatively, efficacy should be equivalent to that of ITNs when deployed in areas of pyrethroid-susceptibility (6). |</p>
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| Entomological efficacy | • Treatment(s) should demonstrate high kill (≥ 80%) of insecticide-resistant mosquito vector(s). The killing effect is required to occur during the extrinsic incubation period of the malaria parasite (i.e.< 10–14 days).  
• Rapid knockdown of Anopheles mosquitoes would be preferable  
• The entomological effect(s) should be achieved for a minimum of three months, with a desired duration of efficacy being that of one year or longer (see section on residual effect / continued efficacy) |
| Mode(s) of action | • Acts preferably on one or more target sites that differ from each other and from that of pyrethroids and organophosphates.  
Note: WHO will utilize the classification used by the Insecticide Resistance Action Committee specifically designed to clarify different modes of action([https://irac-online.org/modes-of-action/](https://irac-online.org/modes-of-action/)). |
| Access and affordability | • The intervention needs to be affordable so that its cost does not constitute a barrier to access, including in low-to middle-income countries.  
• The cost-effectiveness of the intervention should be similar to or better than that of the current standard of vector control in a specific setting. |
<p>| Feasibility | |
| Procurement | • Should be suitable for procurement through global donor mechanisms and by national programmes. |
| Distribution | • Should be suitable for distribution through existing delivery channels, i.e. primarily through top-down delivery channels managed by the national programme or its implementing partners. |
| Application | • Field application of the IRS product should have similar requirements to that of currently prequalified IRS products without the need for additional precaution or technology. For example, the formulation of the product would preferably be suitable for application through a compression sprayer with a standard nozzle. |
| Supervision | • Little to no additional training requirement for health-workers apart from the regular refresher trainings would be preferable. |</p>
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| Safety –human health | • The end use product should not pose an unacceptable risk.  
• Appropriate safety/toxicological information needs to be provided to enable WHO to develop a hazard assessment for the active ingredient and a risk assessment for the final product. When available, WHO may use a hazard assessment by a stringent regulatory authority to inform its own assessment.  
• New active ingredient(s) should preferably be registered by a stringent regulatory authority. |
| Safety –environmental effects, including disposal | • The application of the product should not adversely impact the environment.  
• Biodegradable product containers would be preferable.  
• The product must be stable and suitable for transport and storage at room temperature of tropical areas. |
| Non-target species | • Risks to non-target species should be in accordance with required environmental and ecotoxicology standards at the time of submission for registration. The environmental exposure should be kept to the minimal for IRS products by developing non-volatile compounds. The main issues of concern are non-target insects commonly encountered near/in the domestic environment such as bees and butterflies. |
| Product quality and durability |                                 |
| Residual effect / continued efficacy | • The residual effect of active ingredient(s) in the IRS product should be at least three months. A product would, preferably, remain fully active for an entire year or longer on mud, concrete and wood.  
• The concentration of the active ingredient(s) available on different wall surfaces (e.g. cement, mud/clay, wood) should be sufficient to induce the intended effect throughout the product’s useful life and to reduce the risk of selection for insecticide resistance. |
| Shelf life and storage | • The product should remain fully effective and otherwise retain its quality during shipment and after storage under field conditions for up to 24 months. |
| End user suitability |                                 |
| Community acceptability | • The application of the IRS product should be acceptable to the community. This implies that the application is not offensive to the residents in ways such as generating strong or foul odours, or visible stains on the walls and should not cause any irritancy or skin sensitization  
• Easy to deploy by operators, peripheral health- or aid-workers. |
References