World Health Organization

Preferred product characteristics: endectocide and ectocide products for malaria transmission control

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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 malaria vector control. The PPC published here describes the characteristics of endectocide and ectocide products deployed with the aim of controlling malaria transmission. In this context, endectocides are defined as drugs that kill both endoparasites, such as parasitic worms, as well as ectoparasites that feed on treated hosts. Ivermectin is currently the best studied and most commonly used example of an endectocide in the context of malaria vector control. Besides its broad antiparasitic activity, that has led to extensive use in the control of onchocerciasis and lymphatic filariasis, ivermectin can kill mosquitoes that feed on treated humans and livestock during a dose-dependent period *(2)*. While ivermectin was used as a prototype in the development of an earlier WHO PPC on endectocides *(3),* there are other potential candidates under development / evaluation in this field. Some of these, such as nitisinone, for which activity against tsetse flies has been demonstrated in the laboratory *(4)*, do not kill endoparasites but may provide mosquito control. These types of products will be referred to as ectocides throughout this document.

This and other PPC documents *(5,6)* were developed to address the public health need for additional malaria vector control interventions to close current gaps, such as the lack of tools to control outdoor biting, and to provide options to manage the evolution and spread of resistance to insecticides currently used and deployed. This document is a revision and expansion of the PPC on endectocides published by WHO in June 2017 *(3)*. The update was conducted according to WHO's latest processes for PPC

development to incorporate lessons learned since 2017, reflect on latest research in the field, and to ensure alignment in structure and content with other PPCs for malaria vector control where such alignment is justified.

Terminology

Area under the curve (AUC) is a term used in the field of pharmacokinetics to describe the region under a plotted line in a graph of medicine concentration in blood plasma over time. Typically, the area is calculated starting from the time the medicine is administered until the time when the concentration in plasma is insignificant. The area under the curve represents the total exposure that the body receives to an active substance and helps to evaluate and compare bioavailability profiles between medicines. The time at which the highest concentration of the active substance is found in the blood is called **Tmax**, and the maximum concentration of the active substance found in the blood stream is called **Cmax**.

Endectocide A drug effective against both endoparasites and ectoparasites

Ectocide A drug without established activity against endoparasites that is effective at killing haematophagous ecto-parasites once these have ingested one or more blood meals from a treated host (human or animal)

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 of research and development and public health priorities. PPCs accommodate a number of target product profiles (TPPs). The preferred product characteristics should reflect the ideal characteristics required to rapidly and effectively achieve a global health impact.

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.

Endectocide and ectocide products for malaria transmission control

Background and purpose

The recognition that a drug originally shown to kill endo- and ectoparasites may provide a useful addition to the existing set of malaria vector control interventions is based on decades of research demonstrating effects on anopheline mosquitoes once these have fed on treated hosts. *In vitro* studies have shown that ivermectin kills *Anopheles* that ingest sufficient doses in a blood meal, and also causes numerous sublethal effects *(7-11)*. These results have been confirmed in clinical studies using membrane *(12)* and direct feeding *(13)* methodologies. Modelling based on these studies indicates that MDA with ivermectin has the potential to reduce malaria transmission *(14)*, mainly by negatively impacting mosquito survival, fitness, and fertility, and potentially inhibiting sporogony. Work on other drugs that lack activity against endoparasites but that may have effects on mosquitoes comparable to ivermectin is at a much earlier stage *(4)*, but it is recognized that this approach may also be of value.

This PPC was updated to acknowledge WHO's continued identification that endectocides for malaria vector control are an as yet unmet public health need, to update the preferred characteristics of such interventions where required and to expand them to ectocides. Since the publication of the first WHO PPC on endectocides in 2017, the evaluation process for new vector control interventions has evolved, and a provisional intervention class to accommodate endectocides and ectocides has been created *(15).* It is anticipated that product developers and researchers will draw on this information to develop a range of TPPs for products in this potential intervention class. The PPC will continue to be a dynamic document that will be updated as new data indicate the need to make changes to the associated parameters and characteristics and/or to the identified public health need itself.

Parameter	Preferred product characteristic
Indication	
	• Reduces or prevents infection and/or disease caused by *Plasmodium* in humans. • Suitable for use by all age groups, including women of child-bearing age, pregnant and lactating women, and children under 5 years of age.
Target population – human	
	• Populations at risk of malaria.
Target population – disease vector	
	• *Anopheles* malaria vectors, including populations resistant to insecticides in current use. The current priority is for products that effectively control pyrethroid- and/or organophosphate resistant mosquito populations. • Control of other arthropod disease vectors, nuisance-biting arthropods and/or intestinal parasites is considered an added advantage.
Epidemiological efficacy	
	• Protective efficacy to reduce or prevent malaria infection and/or disease in humans.
Entomological efficacy	
	• Treatment(s) should demonstrate high kill of mosquito vector(s) and be assessed based on the time over which a sustained plasma concentration continues to provide 50% kill (i.e. the LC_{50}) • The LC_{50} should be maintained in individual hosts for the duration of at least one month after mass drug administration has been delivered to the target population • Rapid knockdown of *Anopheles* after ingestion of a blood meal from a treated host would be preferable, as would be additional impact in terms of reducing vector fecundity
Dosage, schedule & formulation	
	• The cumulative administered human dose (mcg/kg/day) that most closely achieves the desired area under the curve (AUC) needed for the efficacy target • C_{max} below the theoretical mosquito LC_{99} • Timed to cover malaria transmission season • Single-dose administration of a slow-release formulation to sustain the mosquitocidal effect over time may be preferred, as it could facilitate programmatic delivery. Risk-benefit analysis will be required to evaluate longer residual efficacy against potential risk factors such as the impact of a longer half-life drug on toxicity or development of vector or parasite resistance • Oral tablet(s) given monthly or less often or slow-release injectable or non-injectable formulations for single dose administration or long elimination half-life
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.

Parameter	Preferred product characteristic
Feasibility	
Procurement	• Should be suitable for procurement through global donor mechanisms and by national programmes.
Distribution/Application	• Should be suitable for distribution through existing delivery channels, namely through the currently WHO recommendations for MDA including minimum requirements for dose determination during the distribution in limited resource settings.
Supervision	• Little to no additional training requirement for healthcare providers would be preferable.
Regulatory	
Safety – human health	• The end use product should not pose an unacceptable risk. • Strategy available for risk minimization in specific high-risk situations (e.g. the need for such strategy to allow ivermectin administration in *Loa loa* endemic areas). • Be accompanied by a well-established and straight-forward protocol (affordable in limited resources settings) for managing and responding to adverse events.
Registration / prequalification	• New product(s) are approved and licensed by a stringent regulatory agency and/or prequalified by WHO • Preferably to have more than one supplier with approval from a stringent regulatory authority or prequalified by WHO
Safety – environmental effects, including disposal	• Use, disposal or degradation of the product should not pose an undue environmental hazard.
Drug–drug interactions	• No significant interaction with antimalarials, antiretrovirals, TB drugs, antihelminthic and common over-the-counter drugs
Interactions with existing vector control interventions	• The endectocide/ectocide intervention should demonstrate no antagonistic effect to existing vector control interventions where it is deployed alongside any of these other interventions
Product quality	
Residual chemical content and continued efficacy	• The treatment(s) should demonstrate high kill of mosquito vector(s) and be assessed based on the time over which a sustained plasma concentration continues to provide 50% kill (i.e. the LC_{50}). This minimum killing effect of female anopheline mosquitoes should be achieved within three days from a blood feed. • The LC_{50} should be maintained in individual hosts for the duration of at least one month after mass drug administration has been delivered to the target population
Shelf life and storage	• Stable for at least 60 months at 37 ºC and 75% humidity • The product should remain fully effective and otherwise retain its quality during shipment and after storage under field conditions for up to 24 months.
Packaging and presentation	• The product must be stable allowing for safe transport and for storage at room temperature of tropical areas

Parameter	Preferred product characteristic
End user suitability	
Community acceptability	• Acceptable in all age groups including children 5–15 kg, women of reproductive age without a pregnancy test, pregnant women, and in lactating women.

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