DETERMINATION OF EQUIVALENCE FOR PUBLIC HEALTH PESTICIDES AND PESTICIDE PRODUCTS

Report of a WHO consultation

Geneva, Switzerland

17–18 October 2016

WHO/HTM/NTD/WHOPES/2017.1

Suggested citation. Determination of equivalence for public health pesticides and pesticide products. Report of a WHO consultation, Geneva, Switzerland, 17–18 October 2016. Geneva, Switzerland: World Health Organization; 2017 (WHO/HTM/NTD/WHOPES/2017.1). Licence: CC BY-NC-SA 3.0 IGO.

Cataloguing-in-Publication (CIP) data. CIP data are available at http://apps.who.int/iris.

Sales, rights and licensing. To purchase WHO publications, see http://apps.who.int/bookorders. To submit requests for commercial use and queries on rights and licensing, see http://www.who.int/about/licensing.

Contents

1. Summary

On 17–18 October 2016 the Department of Control of Neglected Tropical Diseases, the Global Malaria Programme and the Prequalification Team of the World Health Organization (WHO) convened an expert consultation with the following objectives:

- to discuss the outcomes of a WHO informational session on determination of equivalence for pesticide-based vector control products held on 1–2 February 2016;
- to further understand the perspectives of pesticide manufacturers on the current equivalence criteria and procedures established jointly by the Food and Agriculture Organization of the United Nations (FAO) and WHO; and
- to advise on the FAO/WHO criteria, procedures and data requirements for determination of equivalence for public health pesticide products.

The meeting reviewed the current WHO parameters and criteria for the evaluation of public health pesticide products within four main categories for which WHO has long established their public health value, namely: long-lasting insecticidal nets (LLINs), insecticides for indoor residual spraying (IRS), mosquito larvicides, and insecticides for space spraying. The meeting discussed the FAO perspectives on equivalent pesticides for agricultural use, procedures for listing equivalent medicines under prequalification by WHO, and determination of equivalence from a country-level regulatory perspective in Chile, Kenya, India, the European Union and the United States Environmental Protection Agency. The perspectives of both innovator industries and generic industries were considered during the open session. The closed meeting scrutinized current WHO procedures and criteria for determination of equivalence for generic public health pesticides.[1]

Draft recommendations to WHO

The experts noted that protection of human health and access to high-quality products for public health are the highest priority for WHO. Quality assurance for all public health pesticide products should be emphasized.

The main conclusions and recommendations of the meeting were as follows:

1. Pyrethroid-based long-lasting insecticidal nets

The bioefficacy of equivalent nets (candidate LLINs) should additionally be evaluated using the cone bioassays (and, if required, tunnel tests) after washing them 20 times or more according to the product claim, following the same "field" wash procedure as is currently recommended for Phase II (experimental hut trials); the bioefficacy should be compared in parallel with similarly washed comparator (reference) LLINs.

2. Insecticides for indoor residual spraying

Laboratory (Phase I) efficacy and residual activity on relevant substrates (e.g. mud, cement, wood) should be tested for all IRS formulations, including those with slow-release properties. Concurrent

[1] Manual on development and use of FAO and WHO specifications for pesticides. Geneva : World Health Organization ; 2016 (http://apps.who.int/iris/bitstream/10665/246192/1/WHO-HTM-NTD-WHOPES-2016.4-eng.pdf, accessed January 2017).

comparative assessment of a generic (equivalent) product with a comparator (reference) IRS product is needed to avoid any confounding local factors and conditions between the present tests and those originally done for the evaluation of the reference.

Insecticidal efficacy (knockdown and/or kill) of generic products should be higher or similar, while the residual activity should be the same as or longer than that of the reference product.

Quality control testing is currently required for the reference formulated product; similar testing should be done for the generic product when tested in Phase I for compliance with the WHO specification for the reference.

3. Mosquito larvicides

Simulated efficacy evaluation under laboratory conditions should be made for the generic product compared with the reference formulation according to the procedure described in the WHO guidelines for evaluation of mosquito larvicides.[2]

4. Space spraying products

If the generic product is within the WHO or manufacturing specifications for the reference product, no efficacy data are required for assessment of the generic products; if, however, they do not comply with the reference specification, it would be considered a non-equivalent product.

General recommendations

The following general recommendations were made:

- *According to the International Code of Conduct on Pesticide Management, manufacturers should provide samples of recommended reference products for quality testing and research and development purposes. The reference products should comply with WHO or manufacturing specifications.*
- *No changes in the FAO/WHO Manual on pesticide specifications are required to be made as the efficacy test data are not considered for establishing pesticide product specifications, which are based on physical and chemical properties.*

Additional details on the findings of this consultation are contained in the full meeting report.

[2] Guidelines for laboratory and field testing of mosquito larvicides. Geneva: World Health Organization; 2005 (http://whqlibdoc.who.int/hq/2005/WHO_CDS_WHOPES_GCDPP_2005.13.pdf, accessed January 2017).

2. Background and opening statements

An expert consultation on the determination of equivalence for pesticide-based vector control products was organized at the Hotel Intercontinental in Geneva, Switzerland on 17–18 October 2016. The meeting was convened to address the outcomes of an informational session held at WHO (Geneva, 1–2 February 2016) The purpose of the informational session was to inform key stakeholders of FAO/WHO's definition and criteria for determining equivalence of pesticides within the framework of the International Code of Conduct on Pesticide Management and on WHO's equivalence process for evaluation of medicines with the goal of determining how this equivalency process could be used in evaluating pesticide products for use in vector control.

The objectives of the present meeting were:

- to discuss the outcomes of the WHO informational session on determination of equivalence for pesticide-based vector control products (Geneva, 1–2 February 2016);
- to further understand the perspectives of pesticide manufacturers on the current FAO/WHO equivalence criteria and procedures; and
- to advise on the FAO/WHO criteria, procedures and data requirements for determination of equivalence for public health pesticide products.

Dr Dirk Engels, Director, WHO Department of Control of Neglected Tropical Diseases, opened the meeting by stating that WHO's agenda for vector control is shared by the Department and the Global Malaria Programme; collaboration is strong. Earlier in 2016, a consultative meeting was held to inform stakeholders of the rationale behind determination of equivalency and to seek their advice on and experiences of use with the process. As per WHO proceedings, expert consensus is requested on several of the points raised to advise WHO on policy for determination of equivalent pesticide products. Innovative products are needed, and their development comes at a cost for the developers. Striking the right balance between innovation and pricing of products is important to ensure access to vector control commodities while also maintaining investments in vector control. The open session would allow input from stakeholders and the closed session would allow experts to formulate advice for WHO.

Dr Pedro Alonso, Director, WHO Global Malaria Programme, described the interests of the Programme in vector control, particularly in light of recent unprecedented progress in the use of vector control to target malaria vectors. As vector control is a critical health intervention for many diseases, WHO has launched a global vector control response that aims to reenergize and reposition vector control within policy frameworks as a core public health intervention. New tools are needed to address many challenges for vector-borne diseases. Generic manufacturers also play an important role in ensuring access to vector control products. A balance is needed between innovation and access to vector control, and any conflicts must be managed to ensure the best advice to WHO.

Dr Raman Velayudhan, Coordinator, Vector Ecology and Management, WHO Department of Control of Neglected Tropical Diseases, presented the draft agenda and objectives of the meeting.

The meeting was convened in open and closed sessions (Annex 1) and attended by invited experts, FAO, representatives of the pesticide industry and members of the WHO Secretariat (Annex 2). Dr Markus Müller was appointed as Chairperson and Dr Anna Drexler and Dr Emmanuel Temu as Rapporteurs. The agenda was reviewed and adopted.

3. Declarations of interest

As per WHO procedure, all the invited experts completed a form of declaration of interests for WHO experts before the meeting, which was assessed for real or apparent conflicts by the WHO Secretariat.

The following interest was declared:

Dr Olivier Pigeon's research centre has received prescribed standard fees from 13 manufacturers of pesticides (Arysta, BASF, Bayer, Christiansen, Gharda, Gowan, Monsanto, Sharda, Shobikaa Impex, Sumitomo, Tagros, Tana Netting and Vestergaard) to meet the costs of research studies on the physico–chemical properties of their respective pesticide products.

The WHO Secretariat assessed the interests declared by Dr Pigeon and these were not found to be directly related to the topics under discussion at the meeting.

No other significant interests were declared.

4. FAO/WHO procedures on equivalency

4.1 Definition and criteria for determination of equivalence

Dr Markus Müller, current chair of the FAO/WHO Joint Meeting on Pesticide Specifications (JMPS), reviewed the past and present processes and criteria of FAO/WHO for determination of equivalence in pesticide active ingredients and formulated products.

Equivalence under the "old" and "new" procedures

Before 1999 and 2002, specifications for agricultural pesticides (for FAO) and public health vector control products (for WHO) were deemed applicable to products of all manufacturers. No hazard characterization and risk assessment was done for agricultural pesticides.

In 2002, a memorandum of understanding was signed by FAO and WHO, and procedures for specifications were changed. Specifications were deemed applicable only to those materials that had been evaluated for chemical and hazard profile. The extension of this data package to a second manufacturer (reduced hazard data package) was termed "equivalence". This process was primarily designed for conventional (synthetic) active ingredients; special consideration is needed for alternative pesticide products, such as microbial pesticides, which are currently under consideration.

A set of rules guide the determination of equivalence, as laid out in the FAO/WHO Specifications Manual.[3] The basic criteria used to determine equivalence is whether or not the product of a second manufacturer ("M2") is **not worse or worse** than the product "M1" on which the "reference" specification is based. Equivalence is a simple concept but determination may be complex and requires a team of experts in various scientific disciplines.

Data requirements for equivalent products are not identical to originator products. To assess the equivalence of a product from a second manufacturer (M2) with that of M1, data requirements include access to information on manufacturing processes, purity or impurity, and hazard data from M1 and M2. The data are compared in a structured three-step procedure, which considers possible gaps and inconsistencies in the two sets of data. Figure 1 presents an overview of this process.

For formulated products, a formulation is considered to be equivalent if the following two conditions are met:

- the source of the technical materials (TC) or technical concentrates (TK) incorporated into the formulation has been assessed as equivalent; and
- the formulated product complies with all clauses of the existing specification for that formulation.

Additional tests were defined for formulated products in which the release profile is critical for efficacy (e.g LLIN and CS). In all cases, "equivalent" means only that basic characteristics pertaining to quality are shared. It does not mean that products are equally suitable for an application or that they provide equal efficacy.