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.

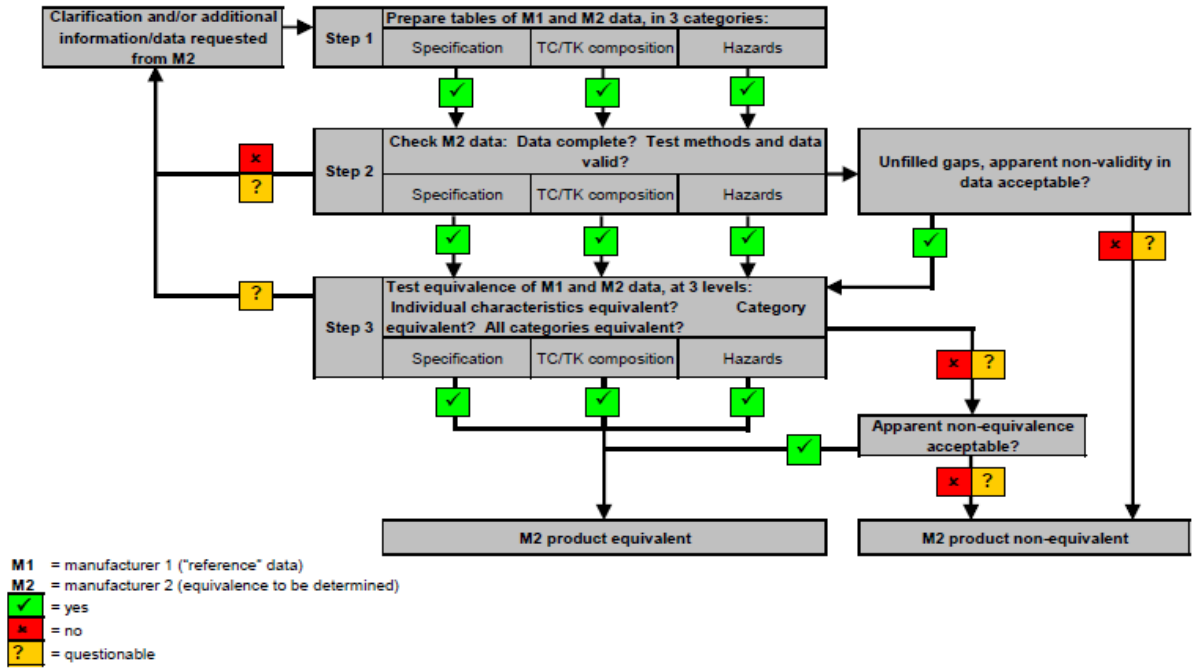
Data requirements for equivalent products are not identical to originator products. To assess the equivalence of a product from a second manufacturer (M2) with that of M1, data requirements include access to information on manufacturing processes, purity or impurity, and hazard data from M1 and M2. The 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.

[3] Manual on development and use of FAO and WHO specifications for pesticides. 2nd edition. Geneva/Rome: World Health Organization/Food and Agriculture Organization of the United Nations; 2010 (http://whqlibdoc.who.int/publications/2006/9251048576_eng_update3.pdf?ua=1, accessed January 2017).



TC/TK, technical materials/technical concentrates

Figure 1. Equivalence determination: overview of the three-step procedure

Overall, equivalence for (chemical–synthetic) pesticides is a proven concept. The active ingredients of pesticides with the same nominal content are expected to deliver the same biological efficacy, but may exhibit different hazard profiles. Guidelines for microbial pesticide specifications are under development, with publication due in 2017.

Discussion

Determination of equivalence measures the specification of the second product against that tested for the first product ("M1"), but the product and regulatory dossier used for the comparison is not known to the equivalent manufacturer.

Also, manufacturers may choose batches of products for use in toxicological studies from pilot scale production; and later, regulators will need to determine whether this batch of product is similar to that used for production quality.

The specification of the test substance used in the toxicological data package is also unknown, and even for current manufacturers, it is not necessary to repeat toxicological testing.

4.2 Review of outcomes from the February 2016 informational session

An informational session on the current procedures used by WHO on determination of equivalence for pesticide-based vector control products was organized by WHO at the Intercontinental Hotel in Geneva, Switzerland, on 1–2 February 2016.

The primary objective of this meeting was to inform stakeholders of the FAO/WHO definition, criteria and requirements for determining equivalence of agricultural and public health pesticide products under the framework of the International Code of Conduct on Pesticide Management.[4] Participants were also briefed on WHO equivalence processes for medicines within the WHO Prequalification Programme.

A secondary objective was to provide a platform for discussion between stakeholders with diverse perspectives on determination of equivalence criteria and processes, and to generate ideas on potential paths forward towards consensus under the FAO/WHO JMPS framework on equivalency determination. Presentations were made by stakeholders in vector control including national regulatory agencies, vector-borne disease control programmes, procurement agencies and both generic and originator industry representatives.

This informational session served to stimulate technical discussions on how the equivalency process can be further strengthened and new ideas on building an environment that supports innovation, promotes quality and offers access to high-quality vector control products to all who need them.

The following conclusions and suggestions from stakeholders were made.

General considerations

In general, equivalency is positive to public health; however, there are issues of fairness and competitive advantage, which stakeholders would like to address. There is very little disagreement on what equivalency is, but there are different expectations on the data requirements and the purpose of equivalency.

The current determination of equivalence process is generally sound; however, there are technologies where the efficacy is based on extended release of active ingredients which may require additional test considerations. Such technologies may be able to leverage regulatory procedures in parallel fields (for example, slow release contraceptive devices). For all products, a better understanding of the manufacturing process can lead to quality assurance and will improve correlates for performance.

Answers are needed on questions such as:

- What bridging studies can help better understand field outcomes and variability?
- What are the impurities that impact safety and efficacy?
- How do we better characterize slow-release profiles?
- How do we maintain confidence in the product from when it is taken off the shelf to the end of its use?

The meeting made the following suggestions to WHO

1. Inclusion of additional efficacy data requirements for equivalency.

4 The International Code of Conduct on Pesticide Management. Geneva/Rome: World Health Organization/Food and Agriculture Organization of the United Nations; 2014 (http://who.int/whopes/recommendations/International_Code_of_Conduct_on_Pesticide_Management_Y2014.pdf, accessed January 2017).

- For LLINs, additional testing is required for interim (Phase II) and full (Phase III) recommendations
- Explore durability criteria when nets are distributed in the field for full recommendation of LLINs.
- Use of pass or fail criteria only after durability tests are validated and accepted by WHO.

2. For IRS products, additional testing (Phase II) for full recommendation of generic products.

3. For space spraying and larvicides, additional testing (Phase II) for full recommendation of generic products.

4. Development of robust quality assurance (QA) process including overall manufacturing process for both originator and equivalent products submitted for evaluation, involving:
   - post-marketing evaluation (including post-marketing variations) of products;
   - post-launch monitoring and surveillance; and
   - field testing for insecticidal efficacy.

5. Identification of research needs for validation, development and addition of laboratory test methods for end-use product specifications to evaluate long-term efficacy and stability for slow or controlled release originator and equivalent products.

Ways forward may include convening a working group of experts and interested parties to further discuss the suggestions made above and finalize WHO recommendations on data needs for equivalent vector control products. This could then become a part of the FAO/WHO Manual for specification requirements.

Suggestions for consideration include:

- Additional manufacturer requirements for JMPS review for insight into how material is produced and the manufacturing process for quality assurance.
- How to incorporate feedback of data on operational use of products from countries.
- Adding components to equivalency process and impact on time to market due to added work for manufacturers and evaluation committees.
- How to link product quality to manufacturing site, post-marketing quality surveillance and extending WHO testing requirements.

4.3 FAO position on pesticide equivalence

Dr Yong Zhen Yang, FAO Secretariat for JMPS, Plant Production and Protection Division, FAO, discussed the Organization's policies for equivalence determination for chemical-synthetic active ingredients in pesticides. FAO is concerned only with comparisons of physico–chemical and toxicological data between products from originators and second manufacturers. Equivalent relevant and non-relevant impurities should be demonstrated. Tier 2 products will allow some differences in the levels of impurities. For all procedures, guidelines published by the Organisation for Economic Co-operation and Development (OECD) must be followed. The equivalence determination procedures used by FAO are commonly used around the world in both industrialized and non-industrialized countries.

A key difference in the work of FAO and WHO is product end-use. Unlike public health pesticides, efficacy testing is often not relevant for agricultural products, since efficacy may vary considerably depending on the conditions of use. Some countries request efficacy trials to fix use patterns and identify good agricultural practices in countries. FAO is willing to follow JMPS procedures for determination of equivalence. Efficacy is not considered helpful for determination of equivalence for agricultural products.

Discussion

A question was raised on how equivalence is determined for agricultural products, and how FAO handles "fairness" and competition.

JMPS respects international intellectual property and protects confidentiality in components of data package (e.g. only relevant impurities are published, full composition not published or manufacturing process).

The concept of equivalence of technical active ingredients, as set out in the JMPS Manual, is a proven concept and has been adopted by many regional and national authorities worldwide.

The use of efficacy data to determine the equivalence of formulated products, however, is considered unsuitable by FAO since the behaviour and performance in the field of pesticides depends on many factors such as crop variety, pest species and climatic conditions, the quality of application equipment (field sprayer, seed treatment), application time and field conditions (type of soil pH, moisture, microbial organisms). Also, field tests are limited by limited crop seasons.

4.4 WHOPES criteria on equivalence determination

Dr Rajpal Yadav, WHO Pesticide Evaluation Scheme, Vector Ecology and Management, WHO Department of Control of Neglected Tropical Diseases, introduced the equivalency process currently used in the WHO Pesticide Evaluation Scheme (WHOPES).

The International Code of Conduct on Pesticide Management[5] was developed with participation of industry and adopted by FAO and WHO Member States. Article 6.1.7 of the Code states that "Governments should use the principles described in the Manual on …. FAO and WHO specifications for pesticides for determining equivalence of pesticides.'' In this context, equivalence means the determination of the similarity in the impurity and toxicological profile, as well as of the physical and chemical properties presented by supposedly similar technical material originating from different manufacturers, in order to assess whether they present similar levels of risk.

The equivalence process is defined in the FAO/WHO specifications Manual (the "manual").[6]

[5] The International Code of Conduct on Pesticide Management. Geneva/Rome: World Health Organization/Food and Agriculture Organization of the United Nations; 2014 (http://who.int/whopes/recommendations/International_Code_of_Conduct_on_Pesticide_Management_Y2014.pdf, accessed January 2017).

[6] Manual on development and use of FAO and WHO specifications for pesticides. Geneva/Rome: World Health

This manual provides the standard process, unified requirements and procedures, harmonized definitions and nomenclature, technical guidelines and standards applicable to pesticides for use in agriculture and public health. The manual was developed through JMPS through a consultative process that included national programmes and representation by industry at JMPS meetings. The procedures and data requirements are reviewed and revised, if necessary, each year in an annual meeting of JMPS with feedback from the pesticide industry.

Types of products evaluated by WHO

Active ingredients and synergists

- Technical materials (TC)
- Technical concentrates (TK)

Formulated public health products

- Long-lasting insecticidal nets
- Insecticides for indoor residual spraying
- Mosquito larvicides
- Space spray products
- Repellents
- Rodenticides
- Molluscicides

The WHOPES evaluation for reference products includes safety assessment, efficacy testing and development of product specifications. Safety assessments take into account hazards associated with the technical materials as well as those associated with exposure risk for formulated products. Product specifications are developed both for technical materials and for formulated products.

The types of products applicable for determination of equivalence include LLIN, IRS, larvicides and space spray products. Most products proposed for public health are out of patent, and therefore hazard data is not needed but risk assessment (human exposure) must be completed. Currently, WHO does not require efficacy data and human risk assessment for generic products. For LLINs, which are considered formulated products, Phase I (laboratory) testing is required to determine regeneration and wash resistance properties – these procedures are intended to test efficacy, but rather to define characteristics of how the active ingredient functions in the formulated product.

Further details on the current test parameters and changes proposed are given for LLIN products (Annex 3), IRS (Annex 4), space spray products (Annex 5) and larvicides (Annex 6).

Discussion

- This review of WHO policies on determination of equivalence was called to address the concerns of different stakeholders. Manufacturers are concerned with fairness in product evaluation timelines between originator and equivalent manufacturers. Generic producers are

Organization/Food and Agriculture Organization of the United Nations; 2016 (http://apps.who.int/iris/bitstream/10665/246192/1/WHO-HTM-NTD-WHOPES-2016.4-eng.pdf, accessed January 2017).

concerned with access to markets. Procurers and programmes seek assurance that generic products perform equivalently in terms of durability in the field.

- Quality management is an issue that affects generic and originator products, and monitoring and evaluation is needed to ensure compliance with specifications.
- Follow-up questions raised in the meeting included exploring the possibility of a follow-up programme for generic LLINs to determine whether they are efficacious in the field.

4.5 Equivalence in prequalification of medicines

Dr Mubangizi, WHO Prequalification Team, explained the organizational transition process within WHO for pesticide product evaluation from the perspective of the Prequalification Team. He emphasized that data requirements for public health pesticides will not change, but process and responsibility for assessment will. One major procedural shift is that manufacturers will generate their own data at quality-assured test sites. Quality management systems will be put in place to ensure consistency, for example site inspections for manufacturers.

What is a generic drug?

"Pharmaceutically equivalent or pharmaceutically alternative products that may or may not be therapeutically equivalent. Multisource* [generic] *pharmaceutical products that are therapeutically equivalent are interchangeable…."[7]

The concept of a generic drug has existed for a long time. Generic equivalent products must be therapeutically equivalent and interchangeable. Broadly speaking, the common themes require that such a product is sufficiently similar (in a pharmaceutical sense) to a reference or listed product that it can be used in lieu of the reference product, for the same indications, with the expectation that the safety and efficacy profile will be the same under the same conditions of use (established by the bioequivalence criteria). By implication, the generic product "borrows" the safety and efficacy profile of the reference product, making development and access to market considerably faster and cheaper. Generic medicines often have well established quality expectations in compendial monographs, for both active ingredient and finished dosage form, making pharmaceutical development much more straightforward.

"Therapeutic equivalence" = "pharmaceutical equivalence" + "bioequivalence"

Bioequivalence forms the bridge between the comparator and innovator test products. It is necessary in pharmaceutical products because a number of factors can cause differences between reference and test products. Drug particle size, for example, can change the dissolution of the material and its delivery to target sites. Excipients can alter the release properties. Even physical changes such as site of manufacture can impact on formulations produced, for example impact of atmospheric water on tablet dissolution in vivo. Bioequivalence is used to establish that a test

[7] Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part (WHO TRS No. 970, 2012).

formulation has the same rate and extent of absorption as the comparator of the active form (or forms) of a drug substance from a medicine into the systemic circulation. The active form may be a metabolite.

While there are many cases where pharmaceutical equivalence is sufficient, bioequivalence is needed to understand the impact of formulation characteristics (Box 4). This is important for linking a multisource drug product to clinical trial material of the comparator, for important post-approval changes in the marketed drug formulation amd to bridge developmental to-be-marketed formulations.

Pharmaceutical equivalence is sufficient for…	**Bioequivalence is needed for…**
Aqueous solutions • **Intravenous solutions** • **Intramuscular, subcutaneous solutions** • **Oral solutions** • **Optic or ophthalmic solutions** • **Topical products prepared as solutions** • **Aqueous solution for nebulizer inhalation or nasal sprays** • **Powders for reconstitution as solutions and gases**	• **Oral immediate release products** o Critical use medicines/narrow therapeutic range drug products o Documented BA or BE problems related to API o Scientific evidence suggesting polymorphs of API, excipients, and/or processes affecting BA o Non-oral, non-parenteral products designed to act systemically • **Modified release products (including oral formulations, patches, implants, etc.)** • **Fixed-combination products with systemic action where at least one of the API requires an *in-vivo* study**

Bioequivalence criteria and study design considerations were briefly touched on, and how the concentration time curves are overlaid between two compounds. Two medicinal products are considered to be bioequivalent if the rates and extents to which the active form or forms of the drug substance reach the systemic circulation from the two products are so closely comparable that their therapeutic efficacy and safety can be expected to be essentially the same. In conclusion, therapeutic equivalence is a synthesis of pharmaceuticals plus bioequivalence.

4.6 Discussion with AgroCare on outcomes of the February 2016 meeting

Long-lasting insecticidal nets (LLINs)		
	Suggestion of February 2016 consultation	**AgroCare's subsequent suggestions**
	Include additional efficacy data for equivalent LLINs: • Phase I for interim; and • Phase II for full recommendations	Replace in WHO specification guidelines: "retention/release index" of active ingredient (8.21.2.4) and synergist (8.21.2.6) in current Phase I by a bio-test on new versus artificially aged net samples.
	Explore durability criteria when nets are distributed in the field for full recommendation of LLINs. Use of pass or fail criteria only after durability tests are validated and accepted by WHO/JMPS.	Release properties and full-scale field investigations, and efficacy of artificially aged net samples against non-aged samples can be tested in a standardized laboratory environment (exposure of mosquito to artificially aged versus non-aged net samples). The test can be easily standardized and safely performed without highly sophisticated and thus readily available or accessible equipment.
Indoor residual spraying (IRS)		
	Suggestion of February 2016 consultation	**AgroCare's subsequent suggestions**
	Include additional testing in Phase II for full recommendation of generic products. Skip Phase I.	Amend Phase I for full product approval by: a combined I c) + d) test, viz. dose–response established on different materials with varying absorbent characteristics and representative of local construction materials; (possibly) amended with an aged residue testing of RS. Delete a) Topical application on target insect individuals b) Irritancy test (insect flying up from treated surface)

		1 c) Knock-down and mortality in bio-assay on different material blocks (mud, wood, …) *1 d) Dose–response curve (on filter paper assay)*
Space sprays		
	Suggestion of February 2016 consultation	**AgroCare's subsequent suggestions**
	Phase II for full recommendation of generic products.	Equivalence (full approval) based on Phase I data.
Larvicide		
	Suggestion of February 2016 consultation	**AgroCare's subsequent suggestions**
	Phase II for full recommendation of generic products.	Based on Phase II, a simulation trial: treatment of larvae in treated water (as for aquatic laboratory toxicology testing)

Discussion

Differences between the pharmaceutical industry and the pesticide industry were raised in the matter of trade secret protections within each industry (more for pesticides, less for pharma).

Data protection or compensation would not make sense for pesticide specifications. Currently, after evaluation of efficacy, a public assessment report is published with efficacy evaluation data. This is done so that countries can use the data for product registration.

A point was raised to clarify that bioequivalence studies for pharmaceutical products use human volunteers for testing.

5. Perspectives on equivalency from stakeholders

5.1 Perspectives of the industry

Frederic Schmidt, Bayer, raised the topic of the equilibrium between generic industries and innovators industries and the need to find a correct balance between sustaining innovation and affording access to vector control tools. Innovation in vector control goes beyond active ingredients to include new product features. These require time, investment and money. Access and affordable products are needed. The key question is how to find the right balance to stimulate companies to innovate, but also maintain the price structure that the generics industry brings to public health. Because active ingredients are largely repurposed from agricultural uses, intellectual property is difficult to obtain in vector control. One suggestion was made for a time limited or period limited acceptance of generic products, with full data package requirements for products submitted within that time period.

Discussion

JMPS is a scientific advisory body on quality control that seeks to control quality and reduce potential risk. Trade issues and market access are issues for the World Intellectual Property Organization (WIPO), and are not part of the mandate of FAO/WHO JMPS. Data protection should be considered at the national level, since at the level of JMPS this would prevent quality control standards from being applied internationally to all products. Additionally, this would be logistically challenging as the programme of work is published for JMPS one year in advance.

Specifications and efficacy testing are separate processes. When companies apply for equivalence, products must be registered in at least one country; however, registration often does not require evaluation and efficacy data.

Concerns were raised that if data protection is introduced with new trials, this may suppress competition and therefore suppress innovation. Additionally, "innovator" products are not eligible for intellectual property protections, raising questions as to the novelty of these types of innovations.

The concept of equivalence and how can it be scientifically demonstrated is a separate issue from how products get to market. For equivalence, quality, safety and performance should be equivalent. Incentivizing innovation and sustaining market forces is a separate discussion.

Procedural differences between pharmaceuticals and agriculture were discussed at great length. It was concluded that pharmacopoeia and JMPS are similar processes. In each process specifications are assessed based on set principles and made public.

The outcomes of this meeting will be considered when designing procedures for both old and new equivalent public health pesticide products under WHO prequalification.

JMPS currently meets the needs of specifications for both agricultural and public health pesticides. Acceptance of common procedures allows collaboration between WHO and FAO in this area. FAO is satisfied with the procedures for specifications for agricultural pesticides currently, and continues in this inter-agency collaboration as long as the process defined continues to meet the needs for agricultural products.

5.2 Perspectives from national regulatory authorities

Stakeholder perspectives on equivalency processes were heard from representatives of the European Union, Chile, India, Kenya, and the United States Environmental Protection Agency.

5.2.1 The European Union

Olivier Pigeon, Walloon Agricultural Research Centre, reviewed approaches to determination of equivalence of pesticide technical materials in the European Union. Legislation for plant protection products (Regulation (EC) No 1107/2009) and biocides (Regulation (EU) No 528/2012) regulate the assessment of equivalence of technical materials.

European Union legislation on pesticides

Regulation (EC) No 1107/2009
The Commission evaluates every active substance for safety before it reaches the market in a product. Substances must be proven safe for people's health, including their residues in food and effects on animal health and the environment
http://ec.europa.eu/food/plant/pesticides/index_en.htm

Regulation (EU) No 528/2012
Companies must demonstrate that the product is effective and does not present unacceptable risks to human health, animal health and the environment.
http://ec.europa.eu/health/biocides/policy/index_en.htm

A two-tiered approach is taken to determine the equivalence of different sources of technical materials, following the guidance document SANCO/10597/2003. Tier I consists of the evaluation of analytical data. If equivalence can be ascertained from these data, Tier II assessment is not needed. However, if equivalence cannot be established on the basis of the Tier I data, further mammalian toxicity/ecotoxicity is considered, which forms the requirements of Tier II. This approach is intended to cover materials from different sources, as in the following cases:

- When technical material comes from a new or different manufacturer other than the applicant of the reference source.
- When the production is switched from a pilot scale to an industrial scale commercial production, the latter is regarded as a different source.
- When there is a change in the method of manufacture (e.g. process or quality of starting materials) and/or a change of the manufacturing location, and/or the addition of one or more alternative manufacturing locations (production sites).

Impurities are any component other than the pure active substance which is present in the technical material (including components originating from the manufacturing process or from degradation during storage).

- Significant impurities: Impurities that results from process variability in quantities ≥ 1 g/kg in the active substance as manufactured, based on dry weight, are regarded as significant.
- Relevant impurities: All impurities of toxicological and/or ecotoxicological or environmental concern compared with the active substance, even if present in technical material at < 1 g/kg.

For evaluation of equivalence of technical materials, Tier 1 data requirements include basic information on the applicant, producer and chemical including synthetic pathway and specification of purity for the active substances in the final product. Identity and content of additives (such as stabilizers) and impurities must be provided and the analytical profile of at least five representative batches, accountable for at least 980 g/kg. The new source is deemed to be equivalent to the reference source if:

- the certified minimum purity is not lower than that of the reference source (taking into account the ratio of isomers, where appropriate);
- no new impurities are present;
- the limits of relevant impurities, as certified for the reference source, are not increased; and
- the certified limits of all non-relevant impurities, as certified for the reference source, are not exceeded.

Evaluation of Tier 1 equivalence of technical materials can result in a decision that (i) the new source is equivalent to the reference source, therefore no further consideration is needed; (ii) equivalence of the new source to the reference source cannot be established based on the Tier I criteria alone, therefore a Tier II evaluation is required; or (iii) the new source is not equivalent to the reference source because the minimum purity is lower than that of the reference source. In the third case an appropriate risk assessment must be conducted for the new source to determine whether plant protection products containing the technical material will fulfil the safety requirements.

Tier II evaluation primarily assesses whether the impurity profile results in unacceptable increase in the hazards of the material of the new source compared with those of the reference source. Data should rely on available information, and not require new animal testing. The objective of the evaluation is to determine if there is unacceptable hazard increase for the new source as compared with the reference source. The evaluation process consists of assessing the toxicity of impurities and determination of an acceptable upper limit concentration for an impurity of toxicological concern.

Tier II assessment can result in the following outcomes:

- The new source presents no greater hazard; hence it is equivalent to the reference source.
- The new source contains one or more impurities of uncertain (eco)toxicological concern; hence more information is required to assess equivalence (there would need to be strong grounds for requiring new toxicity studies).
- The new source is not equivalent to the reference source because it presents a greater hazard.

Tier II evaluation of equivalence of technical materials also considers ecotoxicity. In analogy to the toxicity evaluation process, the objective is to identify whether there is an unacceptable increase in the ecotoxicity of the new source caused by new impurities and/or significantly increased levels of impurities already present in the reference substance. To that end, if new or increased levels of impurities are present, the applicant must provide a case and/or data to show that the new source is not significantly more ecotoxic than the reference source. If there is evidence that a new or increased level of an impurity will NOT have a significant adverse effect on the ecotoxicity of the new source compared with the reference source, the new source is equivalent to the reference source. However, if there is evidence that a new or increased level of an impurity will have a significant adverse effect on the ecotoxicity of the new source compared with the reference source, the new source is not equivalent to the reference source.

Discussion

Formulations verses technical materials. In the European Union, regulation of formulated products occurs at national level, and in loosely defined "zones". A group of countries with similar climatic zones may share registration, but there may also be country level differences in registration criteria. Some countries will rely on specifications only, while other countries will request more data (e.g. chemical composition of the products).

5.2.2 Chile

Ignacio Figueroa-Cornejo, Chile, discussed requirements to support biological efficacy evaluation of plant protection products. To support their effectiveness, the applicant must submit data from field trials that have evaluated the crop–pest–dose combination. Local trials and efficacy evaluations are conducted by SAG (Servicio Agrícola y Ganadero / Agricultural and Livestock Service) authorized experimental stations. Studies are done in a Chilean environmental study area, and a signed certificate is issued, which is a technical document that describes the trials done and the outcomes.

A schematic of the process for local evaluation of plant protection products is shown below. This pathway may not be applicable for public health pesticides, which are regulated under the Ministry of Health and may have different registration and evaluation processes.

5.2.3 India

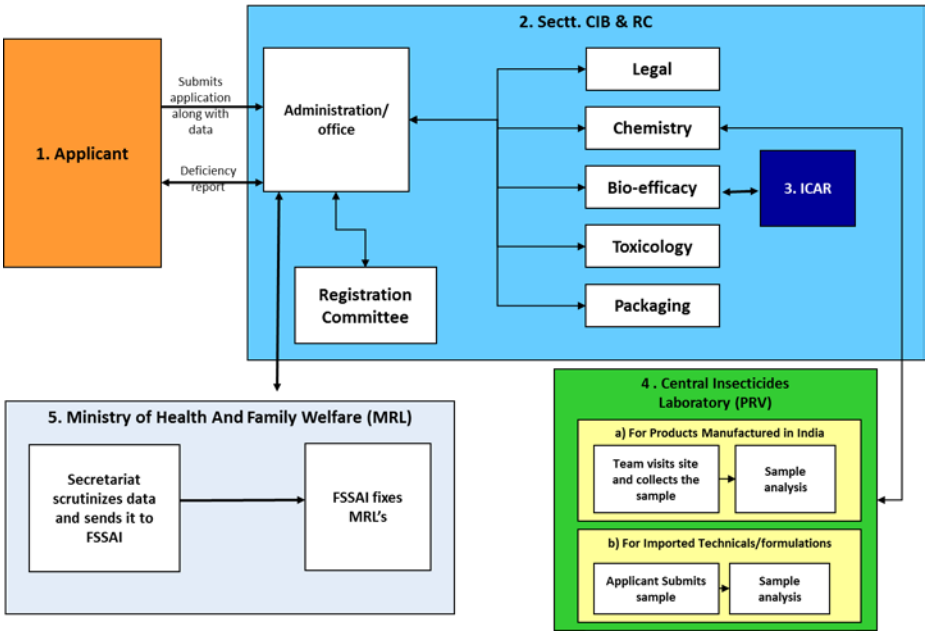
D. D. K. Sharma, India, presented an overview of the Central Insecticides Board and Registration Committee. The insecticides act (1968) was developed with a view to prevent risk to humans, animals and matters connected with the import, manufacture, transport, distribution, stock or sale and use of insecticides. The regulatory structure within India consists of a central insecticide board, with a chairman and 28 members from different ministries, a central insecticides board registration committee (chairman and 5 members); and secretariats of the Board and the Committee with experts in chemistry, bioefficacy, toxicology, packaging and legislation.

REGISTRATION CATEGORIES OF PESTICIDES (INDIA)

- **Provisional registration for two years [Section 9 (3B)] for first time introduction**
- **Regular registration [Section 9(3)]**
- **Me-too registration [Section 9(4)]**
- **Applications could be for import or manufacture**

In the past 5 years (2011–2016), the number of registration applications submitted and certificates issued has increased. To streamline national registration processes, a number of changes were made, including use of online registration systems, elimination of some requirements (renewal licenses, unnecessary forms), harmonization with OECD protocols, and simplification of guidelines for export and biological pesticides.

A schematic of the pesticide registration process in India is given in the diagram below.



CIB, Central Insecticides Board; FSSAI, Food Safety and Standards Authority of India; ICAR, Indian Council of Agricultural Research; MRL, maximum residue level; RC, Registration Committee

Currently, pesticides in India are registered for use in agriculture, public health, household use, and for industrial use. Registration requirements for public health pesticides differ from other categories of pesticide use, e.g. household insecticides. For public health pesticides, laboratory, and small- and large-scale evaluation is required; bioefficacy data are generated by institutes approved by the Indian Council of Medical Research (ICMR) or the Ministry of Health. Chemical equivalence for these products is regulated under the Revised Common Protocol for Uniform Evaluation of Public

Health Pesticides including Bio-larvicides for use in Vector Control (2014). Chemical equivalence is established on the basis of matching of active ingredients (minimum), matching of individual impurities (maximum level), and the absence of any new impurity on a w/w % basis.

5.2.4 Kenya

Barasa Wanyonyi, Lead Expert in Chemistry for the Pest Control Products Board of Kenya, presented an overview of the equivalence criteria for pesticides in Kenya. The Board is a statutory organization of the Government of Kenya established under an Act of parliament – the Pest Control Products Act, Cap 346 Laws of Kenya of 1982 – with the mandate to regulate the importation and exportation, manufacture, distribution and use of pest control products. The decision tree includes the Secretariat (three sections specialists), technical and registration authorities, and a management board. Risk assessment of pest control products is conducted by a subcommittee comprised of associated institutions and a secretariat, and this is reviewed by the Board to issue the Certificate of Registration. Once a certificate of registration has been issued, it is assumed that a risk assessment has been done. Additional requirements may exist.

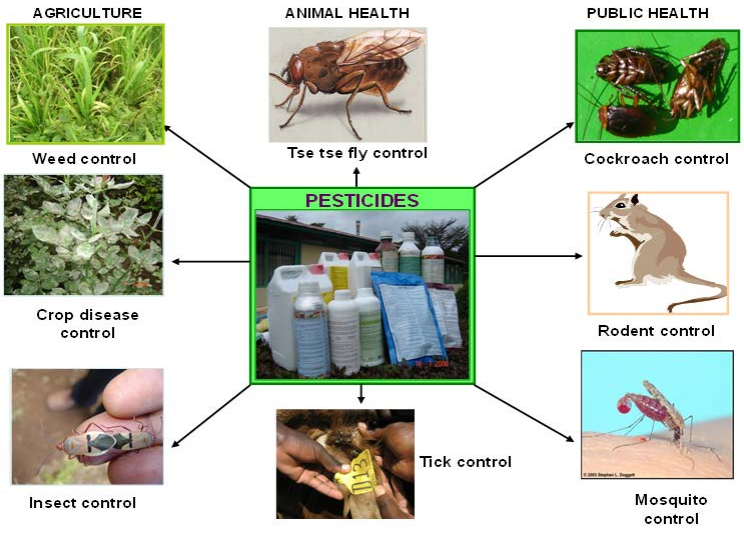


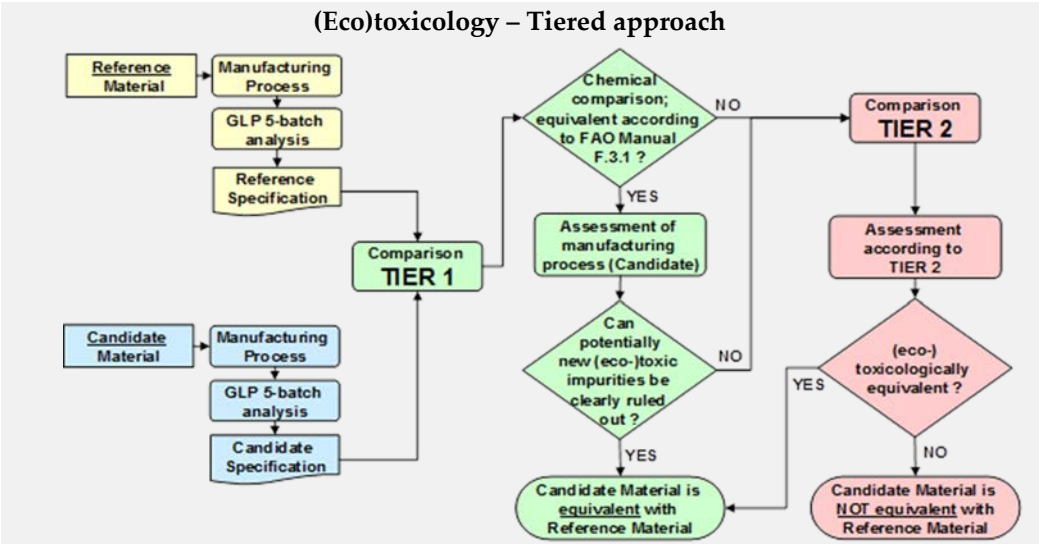
Figure 2. Range of products regulated by the Pest Control Products Board of Kenya

A variety of products are regulated, as shown in Figure 2. The Board has prepared guidelines for conventional chemical pesticides (including for public health), biopesticides (botanicals, biochemicals, microorganisms, natural enemies), adjuvants and wetting agents, technical grade active ingredients, and biocides.

The equivalence process offers the option to evaluate a pesticide against a reference material without having to demand and review the full registration data package. This limits duplicate testing and avoids duplicate work for the registration authority. The Reference Material in this context is defined as the technical grade active ingredient of pest control products that has been extensively tested and evaluated to demonstrate that it is safe to use. The Candidate Material is the technical grade active ingredient of a product for which registration is sought by relying upon the existing registration of a pest control product with alleged equivalent active ingredient(s). The Board relies heavily on standards and guidelines developed by WHOPES (for public health) and FAO (for agricultural products).

The mandatory requirements include methods of manufacture to include raw materials, by products and final products, material safety data sheets for raw materials, physical and chemical properties, and must provide original information in 5-batch analysis studies in laboratories accredited for Good Laboratory Practice. Additionally, the manufacturer must provide original information specific to the generic/product (technical grade) and quality assurance and post-registration surveillance is critical.

A tiered approach is used for ecotoxicology as described in Figure 3.



FAO, Food and Agriculture Organization of the United Nations; GLP, good laboratory practice

Figure 3. Two-tiered approach used to assess equivalency of eco-toxicology of pesticide products for public health, Pest Control Products Board of Kenya

Local bioefficacy is required for both original and generic products, and for laboratory and field studies. These trials are carried out by the Department of Vector Control of the Ministry of Health under local conditions. WHOPES evaluation reports are used, as well as reference standards. All trials are monitored for quality assurance.

The Board requires manufacturers of all formulated products to submit data on physical chemical studies, including MSDS, quality/identity, and composition, and acute toxicity studies to determine safety of the formulated product. These studies are required for both generic and innovator formulation products.

In conclusion, products with the same active ingredient can be registered without repeating the assessment of the full data package while maintaining an acceptable level of safety, if:

- the Reference Material has been evaluated and registered based on the complete data package;
- the Candidate Material is equivalent to the Reference Material; and
- where no complete data set for a Reference Material is available, no equivalence evaluation can be carried out.

By applying the FAO/WHO(PES) equivalence process to Candidate Material, regulators can be assured that products from each and every manufacturer will meet the demanding global standards and quality requirements that are necessary to protect workers, consumers and the environment.

5.2.5 United States Environmental Protection Agency

Bo Davis verbally reviewed procedures for determination of equivalence within the Agency. Data on physico–chemical and acute toxicity form the basis for this assessment. Generic companies wish to rely on the dataset of originator products. This includes chemical datasets, which must be identical; therefore formulations are rarely assessed for equivalency. For acute toxicity, datasets must be similar, not identical. If there are efficacy requirements, efficacy outcomes are also needed, and the formulation type, application rate and claims (use, target, etc.) must be identical to the reference product. The Agency institutes a form of data protection whereby compensation must be paid to originator manufacturers, and evidence presented to the Agency of the compensation offer initiated. The Agency determines the costs of compensation, which is negotiated between companies.

Finally, most equivalence applications use an already approved source; however, in cases of unregistered active ingredients, companies must submit 5-batch analyses to assess the equivalent product.

Discussion

Compensation cannot be commented on by WHO due to the Organization's legal structure, which is not that of a regulatory agency.

JMPS is a scientific advisory board of two organizations that serves as an international reference point for quality control and safety. Its mandate is different for international bodies and national bodies. Companies must submit all data to regulatory authorities, whereas JMPS is a voluntary (not mandated) scheme, and therefore it cannot be compared with national authority data compensation schemes.

Taking fees may be a separate issue from requiring or reviewing any evidence of compensation negotiated or initiated by companies. Operationalization is a separate issue from deciding on the basic requirements for equivalence, which is the subject of the current meeting.

6. Recommendations to WHO

Following the open sessions, closed session discussions involving invited experts only were held to formulate recommendations to WHO on the process for determination of equivalency. The following recommendations were made as a result of these proceedings.

1. 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.

6.1 Pyrethroid-based long-lasting insecticidal nets

According to the WHO guidelines for evaluation of LLINs,[8] the following parameters are currently used for the laboratory (Phase I) evaluation of an innovator ("reference")[9] pyrethroid-LLIN: regeneration time, wash resistance index following a minimum of 20 standard laboratory washes and active ingredient content (with ± 25% tolerance limit of the specification).[10] Phase II is a small-scale field trial for an artificially aged net to understand its efficacy and validate Phase I defined characteristics through field testing in experimental huts. Phase II studies do not measure absolute values of mortality and blood-feeding inhibition but measure relative efficacy of a candidate LLIN compared with a positive control LLIN. The meeting observed that the Phase I and II studies are not designed to determine the operational durability of LLINs in the field, which is the purpose of Phase III testing.

Currently, equivalent LLINs must demonstrate they have identical chemical and physical properties and release characteristics as the reference ("comparator") nets. The chemical and physical properties are defined within WHO specifications. These include description of the LLIN, active ingredient (identity, content), wash resistance index, physical properties (mesh, dimensional stability, bursting strength, weight of netting), flammability and storage stability. Release characteristics are defined in Phase I laboratory testing and include regeneration time and wash resistance index. These must be identical to the reference LLIN for equivalency.

It was noted during the meeting that WHOPES studies show the outcomes of wash resistance and regeneration time bioassays from Phase I to predict Phase II evaluation outcomes for these parameters. Although different wash procedures are used in each of these phases, no data have been presented to WHO to contradict this relationship. However, the meeting considered that given the public health use of nets, additional laboratory tests are warranted to better predict the wash

[8] http://who.int/iris/bitstream/10665/80270/1/9789241505277_eng.pdf

[9] A "reference" profile refers to a WHO/FAO specification that has been established for the first time and which serves as reference for subsequent or equivalent products.

[10] The WHO LLIN guideline (2013) does not mention what laboratory tests are required for evaluation of technical materials (active ingredients) that have knockdown or killing actions, although the tests for new active ingredients with such actions would include: intrinsic insecticidal activity (lethal dosage; lethal concentrations), excito–repellent or irritant properties, cross-resistance to other insecticide classes or mechanisms and the discriminatory concentration.

resistance of equivalent LLINs under field conditions. WHO should consider inclusion of the additional test parameters to specify physical properties of LLINs following review of results from an ongoing inter-laboratory validation of these tests. Furthermore, the added value of the Phase II wash resistance methods (i.e. standard savon de Marseilles or local soap) and of tunnel tests for all nets in Phase I was discussed.

The test parameters for evaluation of LLIN products are summarized in Annex 3. Currently, Phase I efficacy testing is required for equivalence determination as described above. The meeting recommended, however, that:

- 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.

6.2 Insecticides for indoor residual spraying

The test parameters for evaluation of technical materials and IRS products are summarized in Annex 4. These include: (i) tests for the new active ingredient with knockdown or kill actions, namely intrinsic insecticidal activity (lethal dosage; lethal concentrations), excito-repellent or irritant properties, cross-resistance to other insecticide classes/mechanisms and determination of discriminatory concentration; and (ii) efficacy and residual activity of the formulated product on relevant substrates (e.g. mud, cement, wood). In addition, quality control testing of the candidate formulated product for compliance with the WHO specification is also required.

Current criteria and procedures do not require efficacy data for equivalence determination of IRS products. In March 2016, the FAO/WHO Manual introduced a new requirement for formulation with slow-release properties such as the capsule suspension formulations for IRS according to which data are required to demonstrate such slow release properties. By implication, efficacy and residual activity of the capsule suspension formulations for IRS need to be tested in Phase I. To compare minimum data for biological equivalence, the meeting recommended that:

- 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 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.

- the 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 the reference product.

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

6.3 Mosquito larvicides

The test parameters for evaluation of technical materials and formulated mosquito larvicidal products are summarized in Annex 5. Currently, no efficacy data are required for determination of equivalence. The meeting, however, recommended that:

- 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.[11]

6.4 Space spraying products

The test parameters for evaluation of technical materials and formulated products for space spraying are summarized in Annex 6. Currently, no efficacy data are required for equivalence determination. The meeting recommended that:

- if the generic product is within 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.

[11] 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).

Annexes

Annex 1. Agenda

Monday, 17 October 2016 (Open session)

09:00–09:15	Opening of the meeting and welcome remarks - Dr Dirk Engels, Director, NTD - Dr Pedro Alonso, Director, GMP
09:15–09:20	Specific objectives of the meeting and expected outcomes, introduction of participants, and appointment of the Chairperson and Rapporteurs - Dr Raman Velayudhan, Coordinator, VEM
09:20–09:45	FAO/WHO definition and criteria for determination of equivalence and outcomes from the February 2016 informational session - Dr Markus Müller
09:45–10:00	FAO's position on pesticide equivalence - Dr Yong Zhen Yang
10:00–10:15	WHOPES criteria on equivalence determination - Dr Rajpal Yadav
10:15–10:30	Equivalence in prequalification of medicines and outcomes of discussion with AgroCare on outcomes of February 2016 meeting - Dr Deusdedit Mubangizi
11:00–12:30	Hearing of Industry's perspective *(10 min per speaker)* - Discussion
13:30–15:30	Perspectives from National Regulatory Authorities *(10 min each)* - European Union - Chile - India - Kenya - United States Environmental Protection Agency - Discussion

Monday, 17 October 2016 (Closed session for WHO Experts and Secretariat)

16:00–17:30	Discussion

Tuesday, 18 October 2016 (Closed session for WHO Experts and Secretariat)

09:00–17:00	Discussion and finalization of recommendations to WHO on equivalence determination for public health pesticide products
17:00–17:10	Closure

Annex 2. List of participants

EXPERTS

Dr Markus Müller, Federal Institute of Technology, Zurich, Switzerland

Dr Olivier Pigeon, Walloon Agricultural Research Centre, Agriculture and Natural Environment Department, Plant Protection Products and Biocides Physico-chemistry and Residues Unit, Gembloux, Belgium

Dr Yong Zhen Yang, Food and Agriculture Organization of the United Nations, Plant Production and Protection Division, Rome, Italy

Mr Ignacio Figueroa-Cornejo, Servicio Agrícola y Ganadero, Subdepartamento de Tenencia de Tierras y Aguas División Jurídica, Santiago, Chile

Mr Barasa Wanyonyi, Pest Control Products Board, Nairobi, Kenya

Dr Kable (Bo) Davis, United States Environmental Protection Agency, Office of Pesticide Programs, Washington (DC), USA

Mr D. D. K. Sharma, Ministry of Agriculture, Machinery Stores Premises, Directorate of Plant Protection, Quarantine & Storage, Faridabad, India

STAKEHOLDERS

Mr Hans Mattaar, AgroCare, Brussels, Belgium

Mr Michael Carroll, Arysta LifeScience, Slough, United Kingdom

Dr Frédéric Schmitt, Bayer Crop Science, Lyon Cedex, France

Dr Achintya Sen, Clariant Chemicals (India) Limited, Maharashtra, India

Mr Francis Baud, Clariant International Limited, Muttenz, Switzerland

Mr Alfredo Vera Estrada, Labiofam, Havana, Cuba

Mrs Denise Munday, Sumitomo Chemical Agro Europe S.A., Saint-Didier-au-Mont-d'Or, France.

Mr Li Chenbiao, Tianjin Yorkool International, Tianjin, China.

Mr Anand Samiappan, V.K.A Polymers Private Limited, Karur, Tamil Nadu, India

WHO SECRETARIAT

Dr Pedro Alonso, Director, Global Malaria Programme, World Health Organization, Geneva, Switzerland

Dr Anna Drexler, Vector Ecology and Management, Department of Control of Neglected Tropical Diseases, World Health Organization, Geneva, Switzerland

Dr Dirk Engels, Director, Department of Control of Neglected Tropical Diseases, World Health Organization, Geneva, Switzerland

Mr Deusdedit Mubangizi, Prequalification Team, World Health Organization, Geneva, Switzerland

Dr Martha Quinones Pinzon, Entomology and Vector Control, World Health Organization, Geneva, Switzerland

Mr Dominic Schuler, Prequalification Team, World Health Organization, Geneva, Switzerland.

Dr Emmanuel Temu, Entomology and Vector Control, World Health Organization, Geneva, Switzerland

Dr Raman Velayudhan, Vector Ecology and Management, Department of Control of Neglected Tropical Diseases, World Health Organization, Geneva, Switzerland.

Dr Rajpal Yadav, Department of Control of Neglected Tropical Diseases, World Health Organization, Geneva, Switzerland

Annex 3. Current parameters and changes proposed for evaluation of pyrethroid-treated long-lasting insecticidal nets

	Evaluation parameters for reference LLIN	Evaluation parameters for generic LLIN	
		Current criteria	**Changes proposed**
Phase I (laboratory studies)	1. Human exposure risk assessment (HRA)	1. No own HRA required	None; HRA for the reference applies, if equivalent
	1. Regeneration time 2. Wash resistance index (WRI) for at least 20 laboratory washes 3. Active ingredient chemical content (within ± 25% tolerance limit of the specification) 4. For new active ingredients with knockdown or killing action: - intrinsic insecticidal activity (lethal dosage; lethal concentrations) - Excito-repellent or irritant properties - Cross-resistance to other insecticide classes or mechanisms - Discriminatory concentration	1. Regeneration time 2. WRI for at least 20 laboratory washes 3. Chemical content	1. The regeneration time must be shorter or equal to that of the reference LLIN. 2. The wash resistance index should be same as for the reference LLIN. 3. Nominal chemical content must be the same as for the reference; tolerance range does not apply to declared content. 4. Conduct cone test and, if required, tunnel test on nets washed at least 20 times using the same wash procedure as for the experimental hut trials. Use the existing efficacy criteria for the cone or tunnel test.
Phase II (experimental hut trials)	1. Wash resistance 2. Efficacy as measured by vector mortality and blood-feeding inhibition in huts 3. Deterrence or induced exophily rate 4. Chemical content in nets before and after 20 washes, and after testing in huts	No test required at present	None
Phase III (large-scale trials)	1. Long-lasting insecticidal efficacy (up to 3 years) 2. Rate of loss or attrition of nets 3. Physical durability of netting material 4. Community acceptance 5. Adverse events reported	No test required at present	None*

HRA, human risk assessment; LLIN, long-lasting insecticidal net; WRI, wash resistance index

* The *WHO guidelines for monitoring the durability of LLINs under operational conditions* require, however, that durability of all LLINs is monitored in the field and reported (http://apps.who.int/iris/bitstream/10665/44610/1/9789241501705_eng.pdf).

Annex 4. Current parameters and changes proposed for evaluation of insecticides for indoor residual spraying

	Evaluation parameters for reference IRS products	Evaluation parameters for generic IRS products	
		Current criteria	**Changes proposed**
Phase I (laboratory studies)	1. Human exposure risk assessment (HRA)	1. HRA not required	1. None; HRA for the reference applies, if equivalent
	1. Tests for the new active ingredient with knockdown or killing actions: a. Intrinsic insecticidal activity (lethal dosage; lethal concentrations) b. Excito-repellent or irritant properties c. Cross-resistance to other insecticide classes or mechanisms d. Discriminatory concentration 2. Formulated products a. Efficacy and residual activity on relevant substrates (e.g. mud, cement, wood) 3. Quality control testing for compliance with specification that is proposed by the manufacturer, evaluated by JMPS and adopted by WHO)	2. None of the tests are required	1. Comparative insecticidal efficacy and residual activity of the formulated product on relevant substrates (generic versus reference products) – the residual activity should be same or longer; and insecticidal efficacy (knockdown or kill) should be the same as or greater than the reference product 2. Quality control testing of the formulated product for compliance with specification
Phase II (experimental hut trials)	All tests for formulated products: 1. Efficacy and impact on mosquito behaviour in different ecological settings 2. Persistence of residual action on local indoor house surfaces 3. Dosage of application (by chemical analysis) 4. Ease of handing and application 5. Perceived adverse effects	1. No test required	1. No change proposed
Phase III (large-scale trials)	1. Impact on efficacy (e.g. vector density, human biting rate, survival, exophily, entomological inoculation rate) 2. Persistence of residual action on local indoor house surfaces 3. Operational and community acceptance *Note: no epidemiological end-point is measured.*	1. No test required	1. No change proposed

HRA, human exposure risk assessment; IRS, indoor residual spraying; JMPS, Joint Meeting on Pesticide Specifications

Annex 5. Current parameters and changes proposed for evaluation of mosquito larvicides

	Evaluation parameters for reference mosquito larvicides	Evaluation parameters for generic mosquito larvicides	
		Current criteria	**Changes proposed**
Phase I (laboratory studies)	1. Human exposure risk assessment (HRA)	1. HRA not required	1. None; HRA for the reference applies, if equivalent
	1. Biopotency of the technical material (lethal dosage and concentrations) 2. Diagnostic concentration of the technical material 3. Cross-resistance to other insecticide classes 4. Biological activity of the formulated product 5. Assessment of cross-resistance	1. No test required	1. None
Phase II (small-scale trials)	1. Efficacy under different ecological settings 2. Method and rate of application 3. Initial insecticidal and residual activity 4. Effect on non-target organisms	1. No test required	1. Simulated efficacy evaluation under laboratory conditions 2. Tests 2, 3 & 4 not required for generic products
Phase III (large-scale field trials)	1. Efficacy and residual activity 2. Operational and community acceptance 3. Effect on non-target organisms	1. No test required	1. None

HRA, human exposure risk assessment; IRS, indoor residual spraying; JMPS, Joint Meeting on Pesticide Specifications

Annex 6. Current parameters and changes proposed for evaluation of insecticides for space spraying

	Evaluation parameters for reference space spray product	Evaluation parameters for generic products	
		Current criteria	**Changes proposed**
Risk assessment	1. Human exposure risk assessment (HRA)	1. HRA not required	1. None; HRA for the reference applies, if equivalent
Laboratory studies	Tests for the new active ingredient with knockdown or killing action: 1. Intrinsic insecticidal activity by topical application (lethal dosage; lethal concentrations) 2. Cross-resistance to other insecticide classes or mechanisms 3. Discriminatory concentration 4. Insecticidal activity when used as a space spray (wind tunnel test)	1. No test required	1. None
Field studies with formulated space spray product	1. Insecticidal efficacy in controlled indoor setting 2. Insecticidal efficacy in open field (outdoors) 3. Indoor and outdoor large operational trials against wild, free-flying mosquitoes	1. No test required	1. If the product is within specification, no efficacy evaluation is required

Annex 7. Report of a WHO informational session on determination of equivalence for pesticide-based vector control products

Summary

Context

Vector control including use of public health insecticides is an important part of the public health response against vector-borne diseases. The World Health Organization as a global public health organization has strong interests in maintaining the momentum for innovation in vector control and the availability of good quality public health insecticides at affordable cost. WHO specifications for pesticides serve as the international standards for quality control of pesticide products. The FAO/WHO Joint Meeting on Pesticide Specifications (JMPS) advises the two organizations on development of procedures and criteria for development of pesticide specifications, including for generic pesticides through the process of equivalence determination. The concept of equivalence is a technical issue that also has broad implications that should be addressed. To that end, an informational session on the current procedures used by WHO on determination of equivalence for pesticide-based vector control products was organized by WHO in the Intercontinental Hotel, Geneva, Switzerland, 1–2 February 2016.

The primary objective of this meeting was to inform stakeholders of the FAO/WHO definition, criteria and requirements for determining equivalence of agricultural and public health pesticide products under the framework of the International Code of Conduct on Management of Pesticides[12]. Participants were also briefed on WHO equivalence processes for medicines within the WHO Prequalification Programme.

A secondary objective was to provide a platform for discussion between stakeholders with diverse perspectives on determination of equivalence criteria and processes, and to generate ideas on potential paths forward towards consensus under the FAO/WHO JMPS framework on equivalency determination. Presentations were made by stakeholders in vector control including national regulatory agencies, vector-borne disease control programmes, procurement agencies and both generic and originator industry representatives.

This informational session served to stimulate technical discussions how the equivalency process can be further strengthened and new ideas on building an environment that supports innovation, promotes quality and offers access to high quality vector control products to all who need them.

Conclusions

In general, equivalency is positive to public health, however, there are issues of fairness and competitive advantage, which stakeholders would like to address. There is very little disagreement on what equivalency is, but there are different expectations on data requirements and what equivalency is supposed to do.

The current determination of equivalence process is generally sound, however there are pesticide formulation technologies where the efficacy of such products is based on slow release properties which may require additional consideration (for example long-lasting insecticidal nets (LLIN) and capsule suspension formulations). Such technologies may be able to leverage regulatory

[12]http://who.int/whopes/recommendations/International_Code_of_Conduct_on_Pesticide_Management_Y2014.pdf

procedures in parallel fields (for example, slow release contraceptive devices). For all products, quality assurance is important and a better understanding of the manufacturing process will improve correlates for performance.

Next steps

The meeting made the following suggestions to WHO

6. Inclusion of additional efficacy data requirements for equivalency.
   - For LLINs additional testing required for interim (Phase II) and full (Phase III) recommendations
   - Explore durability criteria when nets are distributed in field for full recommendation of LLINs.
   - Use of pass / fail criteria only after durability tests are validated and accepted by WHO.

7. For indoor residual spray (IRS) products, additional testing (phase II) for full recommendation of generic products.

8. For space spray and larvicides, additional testing (phase II) for full recommendation of generic products.

9. Development of robust quality assurance (QA) process including overall manufacturing process for both originator and equivalent products submitted for evaluation, involving:
   - Post-marketing evaluation (including post marketing variations) of products
   - Post-launch monitoring and surveillance
   - Field testing for insecticidal efficacy.

10. Identification of research needs for validation, development, and addition of laboratory test methods for end-use product specifications to evaluate long-term efficacy and stability for slow or controlled release originator and equivalent products.

Ways forward may include convening a working group of experts and interested parties to finalize recommendations on data needs for equivalent vector control products. This could then become a part of the Manual on development and use of FAO/WHO specifications for pesticides[13].

Further suggestions for consideration may include:

- Quality assurance mechanism used as an additional manufacturer requirements for JMPS review for insight into how technical materials and end-use products are produced.
- How to incorporate feedback of data on the operational use of products from countries?
- Adding components to equivalency process and impact on time to market due to added work for manufacturers and evaluation committees.
- How to link product quality to manufacturing site, post-marketing quality surveillance, extending WHO efficacy testing requirements.

[13] Current version available at: http://apps.who.int/iris/bitstream/10665/246192/1/WHO-HTM-NTD-WHOPES-2016.4-eng.pdf, accessed January 2017.

Background and opening statements

The informational session on determination of equivalence for pesticide-based vector control products was organized by the World Health Organization (WHO) in the Intercontinental Hotel, Geneva, Switzerland, 1–2 February 2016. The main subject of the meeting was to disseminate information on the WHO criteria and procedures for the evaluation of pesticide based vector control products developed by original as well as the subsequent (generic) manufacturers who wish to submit their technical materials and/or end-use products for determination of equivalence with the reference products.

Dr Dirk Engels, Director, WHO Department of Control of Neglected Tropical Diseases, opened the meeting by reminding the participants that vector control including use of public health pesticides is and should be an important part of the public health response against vector-borne diseases. The meeting had been convened with the objective to be both informal and informational, fostering innovation in vector control both for malaria and arboviruses disease control. In that way, the Innovation to Impact (I2I) initiative and the Vector Control Advisory Group (VCAG) on new forms of vector control play important roles in informing/advising WHO on the highly needed innovation in vector control. The concept of equivalence of pesticides is on one hand a technical issue, while on the other it has wider bearings that should be addressed.

Dr Pedro Alonso, Director, WHO Global Malaria Programme looked back on the achievements of the last 15 years and informed that a significant proportion of reduction in malaria cases in those years has been due to expansion of vector control. The new Global Technical Strategy for Malaria 2016–2030 adopted by the World Health Assembly in 2015 has set a target of 90% reduction in malaria cases and deaths by 2030. In future, the progress in combating malaria will rely on use of more effective vector control tools. WHO is a global public health organization with vital interests in maintaining the momentum in innovation in vector control. In order to ensure the availability of good quality public health insecticides at affordable prices, generic manufacturers play an important role. The present meeting is expected to deepen the mutual understanding for creating an environment that supports innovation, promotes competition while offering access to quality vector control products to all who need them.

Dr Mark McDonald, Coordinator, Prequalification Team, Regulation of Medicines and other Health Technologies, explained that WHO has now decided to move the WHO Pesticide Evaluation Scheme's current function of evaluation of vector control products to the prequalification scheme in 2017. The Organization has recently received external funding support for this transition, and is pressing forward to initiate the necessary actions. He also stated that this meeting should be devoted to technical discussions how the equivalency process could be further strengthened.

Objectives and outputs

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 equivalence process for pesticides has considerable impact on the availability of pesticide technical materials and pesticide-based vector control products. Key stakeholders in vector control include end-users of products, national regulatory agencies, vector-borne disease control programmes, procurement agencies and both generic and originator industries. The primary objective of this meeting was to inform stakeholders of the FAO/WHO definition, criteria and requirements for determining equivalence of agricultural and public health pesticide products under the framework of the International Code of Conduct on Management of Pesticides. Participants were also briefed on WHO equivalence processes for medicines within the WHO Prequalification programme.

A secondary objective was to provide a platform for discussion between stakeholders with diverse perspectives on determination of equivalence criteria and processes, and to generate ideas on potential paths forward towards consensus under the FAO/WHO JMPS framework on equivalency determination.

WHO is mandated to evaluate safety and efficacy and set quality standards for public health pesticides. This meeting brings together broad stakeholders and experts to exchange information and discuss equivalency related issues and brainstorm potential ways forward. An influx of ideas from stakeholders on the equivalency process could bring to light new pathways that improve access, quality and efficacy for public health vector control.

The outputs from this meeting include:

- Broad understanding among stakeholders of the WHO equivalency process;
- Conclusions and suggestions from the meeting, and
- Dissemination of a meeting report that reflects views of diverse stakeholders in public health vector control.

The meeting was convened in plenary and working-group sessions (Annex 1, Agenda) and attended by the representatives of the industry, institutes and organizations supporting vector control product research and development, government agencies and national programmes, funding and procurement agencies and international organizations (Annex 2, List of Participants). Dr Markus Müller, Chair of the FAO/WHO Joint Meeting on Pesticide Specifications, was appointed as the Chairman and Dr. David Malone, Innovative Vector Control Consortium, as the Co-chair. Ms Susan Jennings, US Environmental Protection Agency, was appointed as the Rapporteur.

Overview of WHO procedures on equivalency

Equivalency for WHO Prequalification of Essential Medicines

Dr Mark McDonald, Coordinator, WHO Prequalification Team, introduced the concept of generic (equivalent) drugs, and the criteria and tests used in the WHO Prequalification Scheme to assess generic drugs.

What is a generic drug?
Generic drugs are drugs that have been deemed therapeutically equivalent to a reference (innovator) drug. After therapeutic equivalence is determined, the expectation is that the safety and efficacy profile of a generic drug will be the same as that of the reference drug under the same conditions of use. By implication, the generic product "borrows" the safety and efficacy profile of the reference product, making development and access to market considerably faster and cheaper. Generic drugs, which are therapeutically equivalent to their reference drugs, are considered to be clinically interchangeable.

The definition of therapeutic equivalence:
Products are considered therapeutically equivalent if they are both pharmaceutically equivalent and bioequivalent.

Pharmaceutical equivalence:
A drug is considered pharmaceutically equivalent to a reference drug when it contains the same composition of active ingredients in the same pharmaceutical form; has the same indications, doses, and routes of administration; and is comparable in terms of quality and safety (usually determined by globally accepted quality control standards, e.g. pharmacopoeias).

Bioavailability and bioequivalence:
Bioavailability is a measure of the rate and extent of absorption of a drug into the human body. If two drugs have equivalent bioavailability, they are considered bioequivalent. Two medicinal products are considered to be bioequivalent if the rates and extents to which the active form or forms of the drug substance reach the systemic circulation from the two products are so closely comparable that their therapeutic efficacy and safety can be expected to be essentially the same.

Bioequivalence studies are tests to determine whether two drugs have equivalent bioavailability, within acceptance criteria set by internationally recognized standards and adopted by the WHO Prequalification team. Bioequivalence studies compare a candidate generic and a reference product and test for formulation related effects on the rate and extent of absorption of the drug substance. The absorption profile of the drug is measured, the critical parameters for which are the maximum concentration of drug in the systemic

circulation (Cmax), the time at which Cmax occurs (Tmax), and the measure of the total systemic exposure over the sampled timeframe (AUC). The bioequivalence acceptance criteria are generally that the 90% confidence intervals of the ratio of test versus reference Cmax and AUC must be in the range 80–125%, with any differences in Tmax falling within clinically acceptable limits.

Specifications for active pharmaceutical ingredients (APIs) and finished pharmaceutical products (FPPs):
Specifications are defined for active pharmaceutical ingredients and finished pharmaceutical products. Tests against these specifications ensure quality and identity of active pharmaceutical ingredients and finished pharmaceutical products, and are used for both reference and generic products. Characterization tests and considerations for active pharmaceutical ingredients include: synthetic route, chemical, physiochemical, and spectroscopic methods (e.g. IR, UV, mass spectroscopy etc.), and discussion of potential isomerism, stereoisomerism and polymorphism (e.g. melting point, diffraction etc.). Typical active pharmaceutical ingredients may be tested against specifications including appearance, identification, melting point, assays, impurities, and particle size. Typical finished pharmaceutical products may be tested against specifications including appearance, identification, assays, content uniformity, and dissolution.

Stability studies:
While specifications allow for testing a finished product or API at one point in time, stability studies must be conducted in order to adequately control the quality of a product throughout its shelf-life. As a result, separate release and shelf-life specifications are set, as drugs inevitably undergo an ageing process when stored. The two specifications are acceptable quality standards for (i) release (after the formulation process) and (ii) at end of shelf-life. Stability studies are usually done by storing a medicine in a temperature and humidity controlled environment for a number of months or years to determine shelf-life (i.e., after what period of time that product no longer complies with its specifications). For these studies, quantitative data are reported where available to allow for assessment of trends.

EXAMPLE FORMAT FOR VECTOR CONTROL PRODUCT ASSESSMENT:

Comments 1: Active ingredient (AI) volumes for vector control and medicine are very different, will this impact the testing process? E.g. will there be issues of heterogeneity in larger batches of insecticide active ingredients?

Response: AI volumes in medicines are quite variable, ranging from large doses to micro dose medicines (e.g. oral contraceptives) with very small active ingredient levels. In general, the batch volume for active ingredients in medicines is likely less than pesticides. There are often more problems with heterogeneity with small batches, due to economy of scale in producing active ingredients.

Discussion

- The focus of the current informational session is on technical criteria for determining equivalence, not on whether the current equivalency processes suppress or promote innovation.

- The equivalency process in medicines is widely regarded as being robust from an efficacy and safety perspective. Bioequivalence studies look at formulation related effects on performance of drugs and are intended to draw parallels between data sets from, for example, originator and generic products. Drug efficacy is demonstrated by originator products through clinical trials and may have no correlation with blood levels of the drug.

- Impurity profiles of medicinal products are often well established through years of use. Safety assessors for new medicines determine what levels of impurities are safe based on evidence that is usually generated through animal safety studies. Manufacturers may use different manufacturing routes to produce the active pharmaceutical ingredients, which can lead to different impurities. The impurity profile can be different for a second manufacturer but the degradation profile should remain similar in the finished products.

- Co-formulants for medicines are subject to less stringent regulations than the API in many countries. For medicines, there are short lists of commonly used inert ingredients. For generic medicines, the aim is typically to produce a product as close as possible to the originator product, and therefore there is not a lot of variability in the co-formulants used.

- Parallels between pharmaceutical equivalence and bioequivalence in assessment of vector control products were discussed, and whether current testing provided sufficient data. For in-use vector control products, establishing duration of protection may be challenging, since LLINs work over years and larvicides and IRS products can have long residual efficacies. Space sprays function more like medicines (e.g. short Cmax). Performance in the field for medicines is demonstrated through studies, or expert advice is used. Some products may not need testing for similarity in field performance, e.g. simple IV solutions.

- Stability and shelf-life studies for drugs are typically ongoing, with companies approved for an initial shelf-life claim, and extending this claim with stability evidence. The same system could be used for vector control products, where an initial shelf-life claim is extended year by year with further testing of the original products

Equivalency for WHO/FAO Assessment of Pesticide Products

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

The specifications (quality standards) for agricultural and public health pesticide products (FAO and WHO, respectively) were first developed independently of each other between 1999 and 2002. In the old procedure prior to 2002, specifications of products were applied to all manufacturers irrespective of whether the products of other manufacturers were evaluated by FAO/WHO. From 2002 onward, the two Organizations joined efforts in the JMPS. In the new procedure, hazard data, physical-chemical profiles and other parameters are evaluated for a product from a specified manufacturer and production process, and summarized in an evaluation report as part of the product specification which is publically made available.

Under the new procedures, the equivalence process evaluates technical materials of subsequent manufacturers compared with the "reference product" of the 1st manufacturer. Specifically, JMPS assesses the physical-chemical profile and some limited hazard data from the data packages submitted by the subsequent manufacturer. If according to the criteria defined in the Manual on Development and Use of FAO/WHO Specifications, the 2nd manufacturer's product is "not worse" than the reference product, equivalence is granted. A formulated product is deemed equivalent, when (1) the product complies with all criteria ("clauses") of the published specification and (2) the technical active ingredient used comes from a source with a valid FAO and/or WHO specification. For agricultural products evaluated in JMPS, FAO does not include information on biological efficacy or risk assessment for equivalence determination. For public health pesticide products, WHO follows the same procedure, however for long-lasting insecticidal nets only, Phase I (laboratory) data are required on regeneration time and wash resistance.

Discussion

- Non-validity in data. This route may be used when there is a lack of clarity in the data package submitted. For example, the classical synthetic route for permethrin produces a toxic intermediate, which is used to form the finished product. This toxic intermediate should be analyzed to show that the level of intermediate is very low. When this test data is not submitted, it may be because the manufacturer did not test it, the intermediate was not used in the synthetic process, or the intermediate was analyzed and was under the limits of detection. Therefore, further feedback is required from the company.
- Non-equivalence in data. This route may be used when there is an alternate synthetic route used. For example, a new synthetic process for permethrin which leads to an impurity profile different from the original manufacturer, though all other parameters remain consistent. Other toxicity data may then be referenced to show that the hazard data is acceptable, leading to a decision of equivalence.
- Choice of Reference Data. Typically the most complete reference profile data package is used. The first manufacturer usually has a full data package on toxicology. Generic manufactures know only what is in public domain (relevant impurities) about the reference product. Many of the manufacturing routes are patent protected, even if the molecule itself is not patent, and reverse engineering may be used to develop new products.

- Formulations. For pesticides, the technical materials or concentrates (TC/TK) are formulated into a final product, and there may be an impact of non-toxicological impurities on performance that should be considered.
- "Not worse" criterion. With pesticides, the "not worse" criterion is used. In medicines, if the product is better, or significantly better, that is an issue.

Equivalency for WHO Assessment of Vector Control Products

Dr Rajpal Yadav, WHO Pesticide Evaluation Scheme, Vector Ecology and Management, WHO Department of Control of Neglected Tropical Diseases, introduced the equivalency process currently used in the WHO Pesticide Evaluation Scheme (WHOPES).

Determination of equivalency in WHO is guided by the International Code of Conduct on Management of Pesticides[14], which was adopted by FAO and WHO member states with voluntary participation of the pesticide industry. The equivalence process, as carried out by JMPS, is defined in the FAO/WHO specifications Manual (the "Manual").[15] The procedures and data requirements are reviewed and revised, if necessary, each year in an annual meeting of JMPS with feedback from the pesticide industry.

The WHOPES/JMPS criteria currently do not require efficacy data and human risk assessment for generic products. For long-lasting insecticidal nets, which are considered formulated products, Phase I (laboratory) testing is required to determine regeneration and wash resistance properties – these are not efficacy testing.

For quality control, WHOPES evaluates and publishes WHO specifications for technical materials/concentrates (active ingredients) and the formulated products for public health viz. long-lasting insecticidal nets (LLINs), insecticides for indoor residual spraying (IRS), mosquito larvicides, space spray products, but also repellents, rodenticides, and molluscicides used for controlling snail vectors. As of February 2016, WHOPES has recommended 11 originator LLINs and 4 equivalent LLIN products. These products may be proposed by original and subsequent manufacturers. Equivalence determination aims to evaluate the purity/impurity and toxicological profiles and physical and chemical properties of proposed technical materials that originate from different manufactures, in order to assess whether they present similar levels of risk.

The value of adding field efficacy data requirement to equivalence determination has been raised by certain stakeholders. Field efficacy trials are limited by the variability both between countries and between sites within one country, making it difficult to use field efficacy data for equivalence. On the other hand, products under evaluation can be characterized in a quality control (QC) laboratory for equivalence. Compliance testing can be done in a QC laboratory as part of the procurement process for both innovator and generic products, in a process similar to testing multiple batches of a reference product.

[14] http://who.int/whopes/recommendations/International_Code_of_Conduct_on_Pesticide_Management_Y2014.pdf

[15] http://apps.who.int/iris/bitstream/10665/246192/1/WHO-HTM-NTD-WHOPES-2016.4-eng.pdf

Equivalency for FAO Assessment of Plant Protection Pesticides

Dr Yong Zhen Yang, FAO Secretariat for JMPS, Plant Production and Protection Division, FAO, Rome presented the cornerstones of equivalence determination for chemical-synthetic active ingredients; the comparison of purity/impurity profile, and physical-chemical properties of pesticide active ingredients. She addressed the participants through a videoconference.

The concept of equivalence of technical active ingredients, as set out in the Manual is a proven concept and has been adopted by many regional and national authorities worldwide. The use of efficacy data for the equivalence of formulated products, however, is considered unsuitable by FAO for the following reasons:

- the behaviour and field performance of pesticides is dependent on many factors like variety (crops), species (pests); climatic conditions etc.
- quality of application equipment (field sprayer, seed treatment);
- application time, field condition (type of soil pH, moisture, microbial organisms)
- Field tests are limited by limited crop seasons

Discussion

- Specification parameter proxies for LLIN durability. LLIN specifications cannot capture all aspects that reflect field performance of LLINs. Preliminary field studies show variable results. "Stronger" nets (e.g. those with higher bursting strength) may have higher rates of hole formation depending upon how they are used and their knitting pattern. Data on the durability monitoring of LLINs in field are not yet available to WHO although a LLIN durability assessment guidelines had been published in 2014.
- WHO recently added three more parameters to LLIN specifications, namely mass of the fabric, modified methodology for flammability test, and a modified method for bursting strength. The weight of the net/m^2 was introduced to ensure uniform weight between LLIN batches with a ±10% tolerance limit. Manufacturers are required to voluntarily disclose the weight of netting and then comply with the specified mass. Manufacturers propose bursting strength in the process of setting WHO specifications. WHO specifies a minimum bursting strength of 250 kPa. Other test methods for quality control of LLINs in the laboratory are being validated to include in LLIN specifications if found suitable. The ability of current and new tests to forecast the durability of LLINs in the field is currently unknown though and will require further studies.
- Costs of originator and generic LLINs. The first manufacturer bears the costs for efficacy demonstration for the originator LLINs. As generics enter the market, the costs of LLINs go down, which may have costs and benefits to different stakeholders. WHO cannot legally prevent manufactures from submitting their products to WHO as active ingredients and polymers used in the products evaluated so far were out of patent. Innovator and generic manufacturers use independent manufacturing processes which are disclosed to WHO but remain confidential.
- Equivalents in agricultural pesticides. For agriculture specifications, such as of deltamethrin, cypermethrin and more, are published on the FAO website and these all

have equivalents. WHO has published specifications for a number of insecticides used for public health vector control, while FAO has published many more for agricultural use, especially for fungicides and herbicides.

- Follow up questions raised in the meeting included exploring the possibility of a follow up programme for generic LLINs to determine whether they are efficacious in the field.

Intellectual Property and Equivalency in WHO

Dr Peter Beyer, WHO Department of Essential Medicines & Health Products presented background information on patents and criteria an innovation has to meet to be patentable. Inventions, whether products or processes, provided that they are new, involve an inventive step and are capable of industrial application (WTO Agreement on Trade-Related Intellectual Property Rights (TRIPS). Minimum term for a patent is 20 years.

Examples of patents in vector control that include inventive steps are:

- Pesticides and combinations by agrochemical companies
- Fabrics, textiles, and their combination by companies specialized in vector control products. LLINs are a mature field of technology, therefore patents mostly cover incremental improvements.

Protection of test data: WTO member countries are obliged to protect undisclosed data submitted for proving the efficacy of new chemical products against unfair commercial use and disclosure. This does not apply to bed nets where older chemical products are used, but is applicable to data that required effort to produce (e.g. Phase I–III). There is no procedure involved in getting data exclusivity. The first applicant has to provide a complete dossier proving safety, efficacy and quality. Subsequent applicants only have to prove quality and bioequivalence, meaning that their product is exactly the same. Certain countries allow this only after a certain period in time (5–10 years), so called data exclusivity. Other countries do not foresee such a time limit. Obligations under WTO TRIPS leave room for different concepts. Data exclusivity delays entry of generic products and thus delays competition, however.

Discussion

- The processes for patent applications are similar whether innovations are considered major or incremental, and patents must be filed in all countries or regions. Data exclusivity can be granted only in the country of application.

- Most patents are from USA, Europe, and China. In China, 10 year patents or longer is available for minor patent applications.

- In some cases, filing a patent is not favoured by manufacturers since even if data exclusivity is granted, proprietary ideas are released to potential competitors. Equivalent products can also be developed through processes that do not violate patency. Companies who file patents must also consider enforcement of any patents once granted.

- Use for data exclusivity in vector control market: In medicines, data exclusivity is usually used for a public good, for example to support investment into products targeting rare diseases / for childhood use. For example, USA gives 6 months additional data exclusivity for pediatric versions of drugs. It is unclear whether this will apply to bed nets, as this is a mature technology in a functioning market.

- Data exclusivity is applied on a country by country basis to protect local companies and is not regulated by international rules or common sense laws. WHOPES is not a market authorization process. Manufacturers can market LLINs not approved by WHOPES, but large scale procurers are guided by WHOPES recommendations.

Perspectives on equivalency: national and programme level

Institute for the Control of Agrochemicals, Ministry of Agriculture, China

Mr Tao Chuanjiang, Health Division, Institute for the Control of Agrochemicals, Ministry of Agriculture (ICAMA), China explained the equivalence principles that are used in China. This presentation was made via videoconference. The equivalence for formulated products is assessed by their composition (active ingredients and co-formulants), and if necessary by assessment of toxicity and ecotoxicity data. The minimum purity in the technical active ingredient must not be worse than in reference material and levels of non-relevant impurities should be within a specified tolerance limit. If new impurities are detected in the generic material, hazard data (mammalian and eco-toxicity) are required before a decision to accept that material can be made. A new Pesticide Administration Regulation will be initiated in the near future and equivalence criteria will be very similar to those as given in the FAO/WHO Manual. All products under registration and re-registration will need risk assessments and only GLP data is accepted for this purpose.

National Health Surveillance Agency, Brazil

Mr Peter Rembischevski, Toxicology Division, Agência Nacional de Vigilância Sanitária (ANVISA), Brazilian Sanitary Surveillance Agency, Brazil gave a brief overview of the scope of the activities of ANVISA and described the equivalence process that is currently implemented for agricultural pesticides. The current equivalence process in Brazil is a three-tiered approach, similar to that described in the European Union guidance document on the process of determination of equivalence of technical materials.

- Tier I – Evaluation of the chemical profile.
- Tier II – Assessment of the acute toxicological and mutagenicity profile.
- Tier III – Evaluation of the toxicological profile with repeated doses and ecotoxicological profile.

Tier-II assessment may also include studies of Structure-Activity Relationships (SAR/QSAR) to evaluate the toxicological relevance of the impurities. For new or increased levels of impurities in the second proposer's material, a battery of *in-silico*, *in-vitro* or *in-vivo* tests with the impurity or technical material are required to assess whether or not the material poses an increased level of hazard compared to the reference material. Products of most applicants fall within Tier I, with approximately 25% of the applications taken to Tier-II, and less than 1% to Tier-III.

Food and Drug Administration, Ministry of Public Health, Thailand

Ms Khun Doolalai Sethajintanin of the Thai Ministry of Public Health, Food and Drug Administration, Bureau of Cosmetic and Hazardous Substances Control, described the

current situation in Thailand. Vector control is regulated under the Hazardous Substances Act of 1992, covering public health pesticides, technical materials and formulated products. For the present, the principles and data requirements of equivalence are understood but not yet implemented in the law. Thailand imports technical grade pesticides to formulate end-use products in the country, and evaluates the completeness and plausibility of the registration dossier. The Thai Food and Drug Administration is building capacity to implement equivalence determination procedures in Thailand.

National Department of Health, South Africa

Dr Patrick Moonasar, National Department of Health, Directorate of Malaria and other Vector-Borne Diseases, gave a brief introduction into the occurrence and seasonality of malaria cases in the provinces and control strategies that are based on indoor residual spraying and long-lasting insecticidal nets. Procurement in South Africa occurs through national or provincial tenders, and WHOPES recommended products are primarily purchased. As generic products tend to be less expensive, special justification and advocacy are required to procure more expensive products. Samples of the product are shipped to an independent laboratory for quality control. For vector control programme consideration in South Africa, efficacy, quality, and cost are the primary concerns when procuring both innovator and generic products.

National Center for Parasitology, Entomology & Malaria Control, Cambodia

Dr Siv Sivannaroth of the National Center for Parasitology, Entomology & Malaria, Control described the malaria control strategy in Cambodia.

Malaria control relies on focal IRS, environmental management and use of LLINs. For IRS, all products used are WHOPES recommended products except DDT. More than 90% of the population has received LLINs, but acceptance is low with only one third of people actually sleeping under them. The main vectors in Cambodia are *Anopheles dirus*, *An. minimus* and *An. maculatus,* which show > 95% resistance to pyrethroids. New combination nets containing pyrethroid synergists and insect growth regulators are expected to be useful to help control resistant vectors.

Federal Ministry of Health, Nigeria

Dr Nnenna Ezeigwe of the Federal Ministry of Health, National Coordinator, National Malaria Elimination Programme (NMEP) spoke via videoconference on the current malaria vector control situation in Nigeria.

There is a high burden of malaria cases in Nigeria, and the National Malaria Strategic Plan (NMSP) for 2014–2020 has the goals to reduce malaria burden to pre-elimination levels and bring malaria-related mortality to zero by 2020. The plan relies on Integrated Vector Management including e.g. distribution of LLINs, rapid scale up of IRS, larval source management (Environmental Management and larviciding), effective case management, e.g. by increased access to malaria rapid diagnosis test and preventive chemotherapy in pregnant women and infants.

The national policy for insecticides relies on defined activities like local field testing of efficacy of products before programmatic deployment/scale-up, post intervention monitoring, IRS spray quality assessment, longitudinal entomological monitoring and quality assurance for vector control commodities. There is a mandatory post-shipment lot testing by the National Agency for Food and Drug Administration and Control Standards of Nigeria. The country relies on WHOPES recommendations, however all vector control products must be registered with NFDAC and have successfully passed the efficacy test can be used.

The policy with regard to innovator and generic vector control products (e.g. LLINs and IRS products) consists of an instructed decision for originator and generic products. For originator products, the following steps are used:

- Overview of specific product properties
- Conduct phase I and phase II studies for LLINs
- Carry out pilot field studies in the local context to collect information on the susceptibility of local vector populations
- Submit tools & results of efficacy trials
- Await outcome/recommendation of evaluation

For generic LLINs and IRS products, the main issues are quality assurance and local acceptability trials to evaluate operational feasibility, ease of hanging for LLINs and other aspects including safety of the products.

Discussion

- Vector control product development needs. The emphasis on vector control in Brazil calls attention to the need for more vector control product development. ANVISA is working to improve procedures for new vector control products. Many companies are registering new products but these mainly target malaria, and are not as useful for Zika due to differences in mosquito biting behavior.
- Capacity building in countries for registration is a priority of the WHO prequalification team, and will be a focus in vector control in the next 2-3 years.

Perspectives on equivalency: procurement

The Global Fund to Fight AIDS, Tuberculosis and Malaria

Mr Azizkhon Jafarov from the Procurement Team of The Global Fund to Fight AIDS, Tuberculosis and Malaria, Geneva gave an overview on the Global Fund's procurement policy on pesticide products.

For pesticide products, the procurement is based on the WHOPES recommended list of products. The Global Fund Secretariat is not mandated to make amendments or adjustments on the recommendation of WHOPES, thus both originator and generic products are eligible for Global Fund procurement. Any changes to distinguish the originator from generic must be reflected in the WHOPES recommended list. Both in 2013 and 2015, Global Fund tenders recognized and considered originator products as an incremental factor in the technical evaluation. In 2015, the weighting of the technical elements increased from 35% to 45%. Originator products receive additional points during evaluation.
Criteria used for originator and equivalent products: Originators are rewarded to reflect the greater investment required. Suppliers who have invested in products which are currently under WHOPES evaluation are scored according to the number of products in the evaluation process. For LLIN procurement in 2014–2016, about 80% of quantities have been allocated to originator suppliers in 2016. A clear trend towards increasing allocations to originator suppliers can be seen. There is a need to ensure an adequate number of suppliers to meet the global demand in a timely manner.

The President's Malaria Initiative

Dr Christen Fornadel gave an overview of the policies of US President's Malaria Initiative (PMI) for procurement of equivalent products. For indoor residual spraying (IRS), all products must have passed WHOPES Phase III evaluation and be on the WHOPES recommended list. If the product is a new formulation, it is eligible for procurement after WHOPES Phase II. In addition, products are selected by chemical class based on the following criteria:

- Susceptibility of local vectors to an insecticide
- Duration of efficacy versus malaria transmission season
- Competitive awards judged on cost, local registration status, toxicity profiles and delivery timeline
- Specific products within a chemical class can be procured provided there is sufficient data and justification.

For LLIN procurement, the product at minimum must have interim status recommendation from WHOPES. PMI applies additional criteria like past performance, financial viability, programmatic consistency and environmental assessments. Current PMI policy states that the equivalency status for LLINs based only on Phase I laboratory studies is insufficient to

determine eligibility for PMI procurement because these studies do not determine how the LLIN product performs under field conditions. PMI has some concerns about equivalency process, due to assessment of limited chemical data and no consideration for durability. PMI conducted durability studies that showed differences in physical durability six months after deployment, likely linked to net weave. This was observed in a particular brand of LLIN that had larger mean hole sizes. The manufacturer changed their weave pattern, but this modification was not covered in WHOPES evaluation. Changes can be made to a product by manufacturers making actual differences in field efficacy, and there is no recognition/provision of that in the current evaluation system.

Equivalency does not ensure manufacturers of comparator LLIN products meet the same QA / QC standards as innovators. PMI also has some concerns that promotion of equivalent LLIN products could negatively impact future R&D of LLINs. Product specific characteristics may have programmatic implications (e.g. variance from standard distribution/ implementation procedures). PMI policy therefore is that comparator products must go through Phase II WHOPES testing before becoming eligible for PMI procurement. Upon completion of Phase II testing, PMI will also assess available data on quality assurance and durability under field conditions. Current market availability is sufficient for current and projected demand, LLINs are currently at historic low prices. PMI welcomes changes to the equivalency process that would ensure quality / consistent field performance while sustaining capacity.

Discussion

PMI Policy on equivalency in LLINs: Current policy states that equivalency status based only on Phase I laboratory studies is insufficient to determine eligibility for PMI procurement because these studies do not determine how the LLIN product performs under field conditions. However, Phase II studies do not provide indication of durability anyway. Phase II is required by PMI with the idea that this requirement will bring equivalents in line with innovator nets, and encourage durability studies to be initiated. PMI requires that durability studies should be conducted for innovator LLINs also.

Differences between equivalent and originator LLIN products could be due to final product manufacturing differences (e.g. weave, AI incorporation) even if the polymer and the AIs are from the same manufacturer.

Utility of laboratory and field studies. Field studies are needed to validate tests in the laboratory. PMI noted differences in some procured LLIN products from the same manufacturer across countries. Field data provided a cross-check for consistency in the product specifications, ensuring that changes had not been made in the manufacturing without notification to WHO. Field study data can be variable, but this data is used for decision-making on efficacy for originator products.

Durability studies. Studies are ongoing to understand whether difference in durability impacts the efficacy of nets. This also may be important with regards to resistance, e.g. in areas of high resistance, durability may be more of a factor. Studies are also in process to

validate first generation laboratory proxies for durability, but these will ultimately need to be correlated with actual field trials.

Equivalent products impact on future R&D: While no data on this was reviewed, the concern was voiced that generic manufacturers do not invest in Phase II or Phase III efficacy testing, therefore the investment required is much greater for innovator manufacturers than for generics.

Industry perspectives on equivalency

AgroCare

Mr Garth Drury presented the perspectives of small and medium sized enterprises (SME/generics) on the equivalency process for vector control products.

AgroCare is an association for generic product manufacturers. Its mission includes ensuring safe and effective standards and encouraging genuine innovation. Just as legitimate competition underpins the affordable supply of medicines in healthcare, the equivalency process also allows for improved access to vector control products. Each unjustified additional barrier to market entry adds costs and time to reach the vector control targets in mostly developing countries. Broad access to LLINs and IRS has contributed to achieving the gains in reducing malaria cases. The current equivalence determination process rewards genuine innovation through patent protection, which can last for 20 or more years for new pesticides. Genuine (non-obvious) and commercialized (non-blocking) innovation should continue to be rewarded and essential safety and efficacy standards met.

Some countries require exactly the same impurity profile as in the (undisclosed) reference products. The AgroCare's view proposed that bioequivalency be required only when chemical equivalence could not be demonstrated. To permit normal free market, conditions means honouring the spirit of patents, but not granting undue extension of patents. Transparency in tenders, standards, and other-discriminatory procurement practices will level the playing field as well as incentivize companies towards real, patent protected innovation.

CropLife International

Dr Helen Pates-Jamet spoke on behalf of CropLife, presenting the views of this organization on the issues relating to equivalence in vector control products. WHO is entitled to determine the level of confidence regarding the data to determine equivalence between original and subsequent manufacturers'' products. For certain vector control products, AI release profile is critical for efficacy. She compared the development costs of innovator LLIN products (within an existing paradigm: > $ 6M, 5 yr time; new paradigm: > $ 10M, 10 yr time), which were much greater than the costs of developing equivalent products (< $ 500K, 1 yr time).

LLINs are complex products in terms of formulation, fabric and sewing technology. Generic products can show differences in some parameters needed to fully describe a LLIN. The assessment for LLIN equivalency is based on Phase I evaluation (wash resistance and regeneration as measured by bioefficacy testing). Current assessment procedures may be inadequate to capture differences between laboratory and field tests, such as mosquito behaviour, production variability, side effects due to formulation differences. For example, bioefficacy studies from Ethiopia with *An. arabiensis* and from the Democratic Republic of Congo with *An. gambiae* in 2012 showed significant differences in knock down and mortality

rates for the vector species between PermaNet 2.0 LN and the equivalent LLIN product used.

For IRS, there may also be differences in parameters between equivalent formulations that are not part of specification for the IRS product and that can affect field performance, e.g., particle size and carrier, differential run off and AI loss on vertical versus horizontal surfaces, effect of natural light, mosquito behavior and spray pattern (particle size, distribution of deposit).

There is a higher cost of innovation including R&D costs, technology, and costs for WHOPES evaluation. There are considerable financial and reputational risks. Creating a level playing field requires incentives for innovator products. In conclusion, more extensive laboratory and field evaluations are needed for "me-too" (equivalent) products to ensure they are properly evaluated and are truly equivalent.

Members of the CropLife vector control group encouraged WHO to foster a balance between innovation and cost–effectiveness for a fair system. Competition, while important, should happen after original products have achieved a return on their investments.

Disease Control Technologies

Mr Andy Butenhoff of the Disease Control Technologies LLC, USA presented an overview on the market entrance of their company which was founded in 2009, and made its first entry with an LLIN product equivalent to Duranet LN. The company has moved from manufacturing equivalent product to an innovator product (Royal Guard LN) that is currently under WHOPES evaluation. Its R&D cost were less than what CropLife has quoted, but WHOPES evaluation costs were the same. Royal Sentry LN is produced by DCT with proprietary master batch formulation. More than 50 million nets have been sold since 2011, and have had zero quality failures (internal COA and pre-shipment inspection) and zero reported failures in the field. Thus there is no evidence to show that its product evaluated through the equivalent process is not the same. Rather this is a success story for public health vector control, having led to increased competition and reduced cost to market.

Both equivalent and originator product approval processes should be re-assessed and improved as necessary to the benefit of public health. Several originator products as well are very different in terms of raw material inputs and production processes than when they were originally tested and evaluated by WHOPES.

Discussion

Post-patent environment. The issue in regards to equivalency is not patents but rather WHOPES recommendations. The company that has developed the technology has gone through a longer and costly process to get the recommendation. The innovators however have a first mover advantage, and must continually move to keep this advantage. The question is whether piggybacking on the investment of innovator companies is appropriate.

Variation reporting and reevaluation. Many companies (generic and innovator) have

common suppliers of raw materials, which can be innovator and generic suppliers. Currently a change of the declared source of polymer, carrier, or AI does not require revisiting the evaluation system and is left to voluntary disclosure.

Adequacy of data to indicate field performance. Data generation required for equivalent products is currently inadequate. The current way of evaluating "me too" products does not tell you how the formulated product would perform in the field. China currently has an efficacy requirement for generic products and will align with FAO/WHO procedures. Innovator industry voiced the opinion that Phase I and phase II studies with follow up in the field for all products should be conducted.

Quality management. There is a myth in medicines that generic products are not as good as originator products, this is not supported by objective evidence. Reports from procurement agencies indicate that both innovator and generic nets have failed in quality checks, often because they are not complying with their own specifications. Manufacturing site inspections and new quality control procedures will help to control quality for both equivalent and innovator products. Post-marketing surveillance is needed to ensure that companies inform JMPS/WHO/FAO of any manufacturing process or site changes, as specified in the Manual.

Efficacy testing and interim recommendations. Time-limited interim recommendations are issued for innovator LLINs after phase II testing and evaluation by WHOPES. WHO supported innovation by not withdrawing these recommendations in spite of delays in starting Phase III evaluation by the innovator manufacturers. Increasing the sample size for phase I for both equivalent and innovator products was important but will increase costs of the trials.

BREAK-OUT SESSION DISCUSSIONS

Background: After the major points of view from registration bodies, programmes, procurement and industry were presented, the meeting participants broke into two working groups to discuss and provide input on the issue of technical criteria for equivalence determination for vector control products. The groups reported back after the breakout session.

Discussion points for the breakout sessions included:

- Concepts from medicines can be used to leverage/support pesticide evaluation, in particular QA/QC issues that are shared by generic and originator producers.
- The definition of equivalency may differ between products intended for short and long-term use. Elements of technology that may be considered include current criteria as well as:
    - Durability specifications (e.g., bursting strength test)
    - Manufacturing process
    - Additional efficacy testing (e.g. Phase I/II, AI release profile during intended period of use (>6 months)
    - Post-marketing quality monitoring
- Operational research and additional data is needed on the performance of originator and equivalent products in the field, including studies to address:
    - Variability of field trial results
    - Bridging studies
    - Evaluation of formulation using slow release AIs
    - Short-term assessment versus long-term efficacy in the field.

Conclusions

GENERAL CONSIDERATIONS

In general, equivalency is positive to public health, however, there are issues of fairness and competitive advantage, which stakeholders would like to address.

There is very little disagreement on what equivalency is, but there are different expectations on the data requirements and what equivalency is supposed to do.

The current determination of equivalence process is generally sound, however there are technologies where the efficacy is based on extended release of AIs which may require additional test considerations.

Such technologies may be able to leverage regulatory procedures in parallel fields (for example, slow release contraceptive devices).

For all products, a better understanding of the manufacturing process can lead to quality assurance and will improve correlates for performance.

Answers are needed on questions such as:

- What bridging studies can help better understand field outcomes and variability?
- What are the impurities that impact safety and efficacy?
- How do we better characterize slow release profiles?
- How do we maintain confidence in the product from when it is taken off the shelf to the end of use?

SUGGESTIONS TO WHO

The meeting made following suggestions for further consideration by WHO:

1. Inclusion of additional efficacy data requirements for equivalency.
    - For LLIN, phase I required for interim recommendation, phase II for full recommendation.
    - Explore durability criteria when nets are distributed in field for full recommendation of LLINs.
    - Use of pass/fail criteria only after tests are validated and accepted by WHO/JMPS.
2. For IRS, Phase II for full recommendation (skip Phase I).
3. For space spray and larvicides, Phase II for full recommendation.
4. Development of robust QA/QC process including overall manufacturing process submitted for evaluation for both originator and equivalent products
    - Post-marketing evaluation (including post marketing variations)
    - Post-launch monitoring and surveillance
    - Field testing.
5. Identification of research needs for validation, development, and addition of laboratory tests for specifications to evaluate long-term durability and long-term stability for slow or controlled release products for both originator and equivalent products.

Next steps

Ways forward may include convening a working group of experts and interested to further discuss the suggestions made above and finalize WHO recommendations on data needs for equivalent vector control products. This could then become a part of the FAO/WHO Manual for specification requirements.

Suggestions for consideration include:

- Additional manufacturer requirements for JMPS review for insight into how material is produced and the manufacturing process for QA.
- How to incorporate feedback of data on operational use of products from countries
- Adding components to equivalency process and impact on time to market due to added work for manufacturers and evaluation committees.
- How to link product quality to manufacturing site, post-marketing quality surveillance, and extending WHO testing requirements.

AGENDA

Informational Session on Determination of Equivalence for Pesticide-based Vector Control Products

1–2 February 2016

Hotel Intercontinental, Geneva, Switzerland

Meeting Objectives

1) Inform stakeholders of the current FAO/WHO definition and criteria used for determining equivalence of pesticide active ingredients and formulations under the International Code of Conduct on Pesticide Management and the WHO equivalence process for evaluation of medicines.
2) Understand the impact of equivalence process on the availability of pesticide-based vector control products.
3) Understand the perspectives of various stakeholders in vector control (end-users, vector-borne disease control programmes, NRAs, procurement agencies, industry) on current equivalence process and the impact of FAO/WHO criteria for equivalence and discuss potential path forward to address any issues.
4) Discuss how equivalency process could be used in the future to improve public health vector control.

	Monday, 1 February 2016 09:00 – 17:30		
1	09:00– 09:20	Welcome remarks	Dirk Engels (NTD) Pedro Alonso (GMP) Mark McDonald (RHT/PQT)
2	09:20- 09:30	- Objectives and outline of the meeting - Appointment of Chair and Rapporteurs	Raman Velayudhan
3	09:30- 10:30	Overview of equivalence used in current PQ process including definition and criteria for equivalence in drugs and proposed quality assurance for pesticide products under I2I initiative	Mark McDonald
		Tea/coffee break	
4	11:00- 11:45	FAO/WHO definition and criteria for determination of equivalence in pesticide products	Markus Müller (JMPS Chair)
5	11:45- 12:30	Equivalency and vector control product assessment in WHOPES FAO's position on criteria for determination of equivalence in plant protection pesticide products	Rajpal Yadav Yong Zhen Yang - *(via Skype)*
		Lunch break	

6	13:30-14:30	<u>Perspectives on equivalency processes - National Regulatory Authorities</u> 1. Institute for the Control of Agrochemicals Ministry of Agriculture (ICAMA), China 2. National Health Surveillance Agency, ANVISA, Brazil 3. Food and Drug Administration, Thailand *Discussion*	Tao Chuanjiang - *(via Skype)* Peter Rembischevski Doolalai Sethajintanin
7	14:30-15:15	<u>Perspectives on equivalency processes - VBD Control Programmes</u> 1. National Department of Health, South Africa 2. National Center for Parasitology, Entomology & Malaria Control, Cambodia 3. Federal Ministry of Health, Nigeria *Discussion*	Patric Moonasar Sovannaroth Siv Nnenna Ezeigwe - *(via Skype)*
		Tea/coffee break	
8	15:45-16:20	<u>Perspectives on equivalency processes – Procurers</u> 1. Global Fund 2. PMI *Discussion*	Azizkhon Jafarov Christen Fornadel
9	16:20-17:30	<u>Perspectives on equivalency process - Industry</u> 1. AgroCare 2. CropLife International 3. Disease Control Technologies *Discussion*	Garth Drury Helen Pates-Jamet Andy Butenhoff
10	17:30-18:00	Summary of feedback from Day 1 and identify open questions for further discussion in break-out session on Day 2	
11	18:00-18:30	Secretariat meeting with Chair and rapporteurs	
	Tuesday 2 February 2016 09:00 – 16:00		
12	09:00-09:30	Recap of open questions and issues for discussion in break-out session on Day 2	Rapporteurs/ Secretariat
13	09:30-10:00	Equivalency and vector control products: Intellectual property aspects	Peter Beyer
		Tea/coffee break	
14	10:30-12:30	**Break-out Session** *Discussion on open questions identified on Day 1 including case studies of equivalence of LLIN and IRS products and potential next steps*	All participants to break out into two groups; each group to discuss all identified issues
		Lunch break	
15	13:30-14:30	Summary of feedback from the plenary session on Day 2 *Presentations of summary by break-out session leads and discussion*	
16	14:30-15:30	Conclusions and closure of the meeting	
		Tea/coffee break	

List of participants

Research and Regulatory

Mr Tao Chuanjiang, Institute for the Control of Agrochemicals, Ministry of Agriculture China, Beijing, China (by Skype)
Dr Deolinda Domingues, Technological Centre for the Textile and Clothing Industries of Portugal, Vila Nova de Famalicão, Portugal
Dr Nnenna Ezeigwe, NMEP, Federal Ministry of Health, Abuja, Nigeria
Ms Susan Jennings, Office of Pesticide Programmes, US Environmental Protection Agency, Arlington, Virginia USA
Mr Francisco Alexandre Shammass de Mancilha, Agência Nacional de Vigilância Sanitária – Anvisa, Brazil
Dr Patrick Moonasar, National Department of Health, Malaria and other Vector-Borne Diseases, Pretoria South Africa
Dr Markus Müller, Agroscope FAW Wädenswil, Switzerland
Dr Olivier Pigeon, Walloon Agricultural Research Centre, Gembloux, Belgium
Mr Peter Rembischeviski, Agência Nacional de Vigilância Sanitária – ANVISA, Brazil
Ms Doolalai Sethajintanin, Food and Drug Administration, Ministry of Public Health, Thailand
Dr Siv Sivannaroth, National Center for Parasitology, Entomology & Malaria Control, Cambodia
Dr Stephen Smith, Centers for Disease Control and Prevention, Atlanta GA, USA

Industry

Dr Bernhard Johnen, CropLife International, Brussels, Belgium
Dr Helen Pates Jamet, Vestergaard, Washington, DC USA
Dr John Lucas, Sumitomo Chemical, London, United Kingdom
Dr William Jany, Clarke International LLC, St. Charles, IL USA
Dr Garth Drury, Rotam CropSciences Ltd, Lyon, France
Mr Anand Samiappan, V K A Polymers Pvt Ltd, Tamil Nadu, India
Mr Ramanathan Natarajan, V. K. A. Polymers Pvt Ltd, Tamil Nadu, India
Mr Andy Butenhoff, Disease Control Technologies LLC, Greer, SC, USA
Mr. Rod Flinn, Disease Control Technologies LLC, Greer, SC USA
Mr David Malone, Innovative Vector Control Consortium (IVCC), Liverpool School of Tropical Medicine, Liverpool United Kingdom

Donors, Procurement and International Organizations

Dr Christen M. Fornadel, President's Malaria Initiative, USAID, Bureau for Global Health, Washington DC USA
Mr Azizkhon Jafarov, The Global Fund to Fight AIDS, Tuberculosis and Malaria, Vernier, Geneva
Dr Jan Kolaczinski, The Global Fund to Fight AIDS, Tuberculosis and Malaria, Vernier, Geneva, Switzerland
Mr Scott Miller, Bill & Melinda Gates Foundation, Seattle, USA
Ms Suzy Nazarro, Bill & Melinda Gates Foundation, Seattle, USA
Dr Dan Strickman, Bill & Melinda Gates Foundation, Seattle, USA

Mr Stuart Turner, UNICEF Supply Division, Copenhagen, Denmark
Dr Ambachew Medehin Yohannes, UNITAID International drug purchase facility, Geneva, Switzerland
Ms Yong Zhen Yang, Food and Agriculture Organization, Rome, Italy
Ms Janet Zhou, Bill & Melinda Gates Foundation, Seattle, USA

Rapporteurs
Mr William Murphy, Boston Consulting Group
Mr Suraj Patel, Boston Consulting Group
Mr Andrew Rodriguez, Boston Consulting Group

WHO Secretariat
Dr Pedro Alonso, Director, Global Malaria Program
Dr Peter Beyer, Senior Adviser, Department of Essential Medicines and Health Products
Dr Anna Drexler, Technical Officer, Vector Ecology and Management, Department of Control of Neglected Tropical Diseases
Dr Dirk Engels, Director, Department of Control of Neglected Tropical Diseases
Dr Mark McDonald, Coordinator, Prequalification Team
Dr Abraham Mnzava, Coordinator, Entomology and Vector Control, Global Malaria Program
Dr Emmanuel Temu, Technical Officer, Entomology and Vector Control, Global Malaria Program
Dr Raman Velayudhan, Coordinator, Vector Ecology & Management, Department of Control of Neglected Tropical Diseases
Dr Rajpal Yadav, Scientist, Vector Ecology and Management, Department of Control of Neglected Tropical Diseases