



Decision Document

Tsara Soft

(Deltamethrin Insecticide Treated Net)

Prequalification Unit – Vector Control Products Assessment (PQT/VCP)

Regulation and Prequalification Department (RPQ)

Access to Medicines and Health Products (MHP)

World Health Organization (WHO)

Prequalification Unit - Vector Control Product Assessment

Decision Document

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1 Introduction

WHO's Prequalification Unit, Vector Control Product Assessment team (PQT/VCP) assesses vector control products and public health pesticide active ingredients to determine their acceptability and that they can be used safely, effectively and are manufactured to a high-quality standard. This is done by assessing product dossiers, inspecting manufacturing sites, and supporting quality-control testing of products. Products that meet prequalification requirements are added to the WHO list of vector control products.

WHO prequalification of vector control products primarily benefits populations most affected by vector-borne diseases by facilitating access to these prevention focused tools. The vector-borne diseases include malaria, and neglected tropical diseases such as Dengue, Chikungunya, Zika, Chagas, Lymphatic filariasis, Leishmaniasis, Human African trypanosomiasis, Onchocerciasis and Schistosomiasis.

This document presents the results of the safety, efficacy and quality (product chemistry and manufacturing process) assessments for the product Tsara Soft and provides the basis for the prequalification listing decision.

2 Product Identification

Tsara Soft is an insecticide treated net (ITN) coated with deltamethrin. At the time of the initial recommendation of the product DawaPlus 2.0 by WHOPES (refer to section 2.1 History of the Submission), the product manufacturing process utilized a tumble dryer approach. The manufacturing method for the product subsequently changed to a stenter process which initially used a single polymer binder, and more recently a blend of polymer binders. The currently declared production method for this product is the stenter process utilizing the blend of polymer binders.

The product is available in 75, 100 and 150 denier (D) versions and has a declared fabric weight of 30, 40 and 42 GSM, respectively. The product has a declared deltamethrin concentration of 80 mg/m² which corresponds to 2.7 g ai/kg net (75D) and 2.0 g ai/kg net (100D and 150D).

The source active ingredient and the declared minimum content is: deltamethrin, declared minimum content 985 g/kg.

The product is formulated in Jiangsu, China and in Lahore, Pakistan.

2.1 History of the Submission

The product Tsara Soft was originally recommended under the name DawaPlus 2.0 following a review by WHOPES in 2009. The product owner of DawaPlus 2.0 was Tana Netting (Thailand) at that time. Subsequently, the product ownership was transferred to a different company, Tana Netting FZ (UAE). In January 2018, in accordance with the procedure established for the conversion of WHOPES recommended products to prequalification listings, the product was prequalified and listed accordingly. In January 2019, Tana Netting FZ submitted a post-prequalification change application to transfer ownership of the product to NRS Moon Netting FZE, and to change the product name to Tsara Soft.

In December 2018 several complaints were submitted by external organizations and Tana Netting FZ, regarding the production of the product and non-compliance with the established specification. An

investigation was launched in early 2019 in response to the complaints. The results of the investigation identified that between the period of January 2017 and April 2018, the third-party manufacturing facility responsible for manufacturing the product was not following the formulation and production process declared to WHO by the responsible applicant. This raised concerns regarding the quality and therefore the residual efficacy of the products manufactured during this time period.

In response to the investigation, NRS Moon Netting FZE submitted information on the restructuring of the affiliated manufacturing site, and validation regarding production of the product in accordance with the declared formulation and production process.

While the initial complaints regarding the product manufactured between January 2017 and April 2018 were being investigated, additional complaints were submitted regarding out of specification findings for products manufactured beyond April 2018. Collectively the product complaints raised concerns regarding the quality, and thereby the efficacy, of the product Tsara Soft and whether the data submitted to the WHO to support the WHOPEs recommendation, and subsequent conversion to a prequalification listing remained valid and were applicable to the current product formulation and manufacturing process. In response to these concerns the prequalification listing for Tsara Soft (PQ Ref # 028-003) was suspended on 12 December 2019. The letter of suspension (Appendix C) outlined the need to conduct a full review of the product including the data package submitted by NRS Moon Netting FZE in December 2019. A complete product dossier was submitted in December 2019.

This information has now been fully reviewed and forms the basis for a decision regarding prequalification of the product Tsara Soft.

3 Assessment of Quality

3.1 Chemical and Physical Properties

Data on the chemical and physical properties of the active ingredient and the product Tsara Soft were provided. These data were obtained from studies conducted according to established standards and/or Good Laboratory Practices (GLP) and are considered complete. Product specific properties are summarized in Table 1.

Table 1 Chemical and Physical Properties for Tsara Soft			
Data Requirement	Test Method	Study Number or Identifier	Result
Active ingredient content	CIPAC M 333/LN/M/(3)	IIBAT Study No.: 19095	Mean percentage of active ingredient present in the net: 75 denier yarn: 2.62-2.78 g/kg Accepted range – 2.025-3.375 100 denier yarn: 2.27-2-37 g/kg Accepted range – 1.5-2.5 150 denier yarn: 1.81-1.91 g/kg Accepted range – 1.5-2.5

Table 1 Chemical and Physical Properties for Tsara Soft			
Storage Stability	CIPAC MT 46.3.4	IIBAT Study No.:19094 No.:19093 No.:19087	Mean percentage of active ingredient present in the net after 14 days at 54 ± 2°C: 75 denier yarn: 98.6% 100 denier yarn: 96.9% 150 denier yarn: 97.8% Accepted value: not less than 95%
Fabric weight	ISO 3801/EN 12127	IIBAT Study No.:19094 No.:19093 No.:19087	75 denier yarn, mean weight: 31.91 g/m ² Acceptable value: 30 g/m ² ± 10% 100 denier yarn, mean weight: 39.49 g/m ² Acceptable value: 40 g/m ² ± 10% 150 denier yarn, mean weight: 45.96 g/m ² Acceptable value: 42 g/m ² ± 10%
Netting mesh size	WHO Specification 333/LN/2	IIBAT Study No.:19094 No.:19093 No.:19087	75 denier yarn, mean mesh size: 24 holes/ cm ² 100 denier yarn, mean mesh size: 24 holes/ cm ² 150 denier yarn, mean mesh size: 14 holes/ cm ² Acceptable values: for 75 and 100 denier yarns the mean value shall be not less than 24 holes/cm ² and the lowest value shall be not less than 23 holes/ cm ² for 150 denier yarn the mean value shall be not less than 14 holes/cm ² and the lowest value shall be not less than 13 holes/ cm ²
Dimensional stability	WHO Specification 333/LN/2	IIBAT Study No.:19094 No.:19093 No.:19087	Acceptable value, not more than 5% All values were under 5%
Bursting strength	ISO 13398-2:1999	IIBAT Study No.:19094 No.:19093 No.:19087	Acceptable values: for 75 denier yarn minimum 250 kPa for 100 denier yarn minimum 350 kPa for 150 denier yarn minimum 420 kPa All values were above the minimum limits.
Flammability	EN 1102:2016	IIBAT Study No.:19094 No.:19093 No.:19087	no ignition, no propagation of the flame

3.2 Manufacturing, Composition and Formulant Information

Data on the manufacturing process and product composition for Tsara Soft have been provided and are adequate. A summary is presented in Table 2. Detailed information on the manufacturing process and product formulation is considered Confidential Business Information (CBI).

Table 2. Manufacturing Process and Product Composition Data Submitted for Tsara Soft		
Description of Starting Material	Confidential Information of NRS Moon Netting FZE – Declaration of Formulation	The manufacturing process utilizes polyester filaments knitted per the specifications and a includes a coating process employing a proprietary mixture of coating agents (binders), deltamethrin, other formulants and water.
Production / Formulation Process	Confidential Information of NRS Moon Netting FZE - Manufacturing Process	Included in the Confidential Business Information.
Discussion of Impurities	Confidential Information of NRS Moon Netting FZE – Quality Dossier	There are no known relevant impurities in the product formulants.
Declaration of Product Formulation	Confidential Information of NRS Moon Netting FZE – Declaration of Formulation	Included in the Confidential Business Information.
Certification of Limits	Confidential Information of NRS Moon Netting FZE – Quality Dossier	2.7 g/kg net ± 25% (75D) 2.0 g/kg net ± 25% (100D and 150D)
Enforcement Analytical Method	deltamethrin	CIPAC N 333/LN/M2/3

3.3 Enforcement Analytical Method

Table 3. Details of the analytical method used to determine deltamethrin in Tsara Soft	
Method ID	Deltamethrin CIPAC N 333/LN/M2/3 for quantification in LLIN

The method is appropriate for the determination of the active ingredient content of the product. This method was validated through the inter-laboratory CIPAC process.

3.4 Specifications

The source of active ingredient is supported by existing WHO specifications.

The specification for the formulated product will be established through the procedures of the WHO/FAO Joint Meeting on Pesticide Specifications (JMPS).

3.5 Impurities of Toxicological Concern

No impurities of toxicological concern were found in the technical active ingredient and other formulants.

3.6 Quality Conclusions

According to the studies provided, all physical-chemical properties of the product were in accordance with the specifications. The proposed methods for assessing the physical-chemical properties of the product were CIPAC methods and/or validated methods. The physical-chemical data were generated in accordance with GLP. A summary of the physical/chemical properties is included in Appendix B.

The quality component of the dossier is considered complete, and the assessment of the submitted information on quality supports prequalification of the product.

4 Assessment of Safety

The applicant submitted an exposure and risk assessment for Tsara Soft, conducted by an independent consultant, based on the WHO 2018 “Generic Risk Assessment Model for Insecticide Treated Nets (GRAM)”.

PQT/VCP conducted a generic exposure and risk assessment of deltamethrin treated bednets based on the highest concentration of deltamethrin currently found in a prequalified ITN and relied on the most conservative default values. The detailed hazard summary and risk assessment may be referenced in the published document: Human Health Risk Assessment, Deltamethrin, An Active Ingredient in Insecticide Treated Nets.

4.1 Safety Conclusions

The potential health risk is acceptable for all populations (adults, children, toddlers and infants) sleeping under a bednet, for adults and children washing bednets, as well as for adults and children both sleeping under and washing the treated bednets (both acute and repeated conditions). The risk ratios are < 1 for all populations, routes of exposure (inhalation, dermal and oral) and all activities (sleeping under, washing, and both sleeping under and washing).

Table 4. Summary of Risk Characterization for Deltamethrin as ITN (up to 3 g/kg or 120 mg/m2)	
Population	Risk Acceptable / Not acceptable
Sleeping Under Net: Inhalation Exposure	
Adult	Acceptable
Children	Acceptable
Toddlers	Acceptable
Infants	Acceptable
Washing of Nets - Acute	
Adult	Acceptable
Children	Acceptable
Washing of Nets - Repeated Conditions	
Adult	Acceptable
Children	Acceptable
Sleeping Under and Washing of Nets - Acute Condition	
Adult	Acceptable
Children	Acceptable
Sleeping Under and Washing of Nets - Repeated Conditions	
Adult	Acceptable
Children	Acceptable
Exposures via Breast Milk from Mothers Exposed to Deltamethrin	
Infants (acute and chronic)	Acceptable
New-borns (acute and chronic)	Acceptable
Combined: Sleeping Under Net and Breast Milk	
Infants (acute and chronic)	Acceptable
New-borns (acute and chronic)	Acceptable

The safety component of the dossier is complete. The assessment of the submitted information on safety supports prequalification of the product.

5 Assessment of Efficacy

5.1 Background

The primary purpose for the use of a pesticide is the control of a pest, which can include a disease transmitting vector. Vector control tools, including formulated pesticides which provide effective management/control of vectors, may be used as part of a resistance management program. Vector control products for use in public health are a component of an Integrated Vector Management

program (IVM). IVM relies on a suite of diverse interventions and implementation of best practices to manage the vector and chemical/behavioral resistance.

A number of efficacy studies were submitted for consideration as part of the current review. These studies examined the efficacy of product which was manufactured using a variety of production methods. As indicated in Section 2 Product Identification, the currently declared manufacturing method is the stenter process. Therefore, based on the findings from the quality assessment of the submitted efficacy studies, only those studies in which the product Tsara Soft was manufactured in a manner determined to be substantially similar to the currently declared formulation and stenter process were considered relevant and deemed acceptable for inclusion in this assessment. The chemical content analysis conducted for each study verified that the tested product samples were in compliance with the specifications and appropriate for use in the study.

The applicant submitted six laboratory studies, four semi-field (experimental hut studies), and three long-term field studies in support of the Tsara Soft efficacy assessment. The semi-field studies were conducted as part of the dossier development for other products, with Tsara Soft ITN included as the positive control treatment. These studies represent the most recently generated data on Tsara Soft in which the product is manufactured utilizing the declared stenter process.

5.2 Summary of Laboratory Studies

The manufacturer submitted reports from six laboratory studies which investigated bio-efficacy of Tsara Soft using standard WHO cone tests on samples of Tsara Soft washed 0, 1, 3, 5, 10, 15, 20 and 25 times. All samples tested using a susceptible lab strain of *Anopheles dirus* performed as expected through 25 washes by inducing either >80% mortality and/or >95% knockdown.

The studies were conducted in 2015, 2016 and 2019 on multiple batches of the product. The data provided on the physical/chemical properties of the samples of Tsara Soft validated the production products used for testing. The chemical content and wash resistance index (90-100%) were found compliant for all samples tested.

5.3 Summary of Semi-Field Studies

Three of the four submitted semi-field studies were considered acceptable for inclusion in the assessment of Tsara Soft. These studies were conducted in Tanzania, Benin and Burkina Faso.

Studies conducted in the semi-field setting often include the investigation of endpoints other than mortality, knockdown and blood-feeding inhibition. Examples of these endpoints include entry rate, exit rate and deterrence, as well as analyses for non-standardized calculations of “personal protection”. Based on existing requirements and the established decision framework, mosquito mortality and knockdown are considered the primary endpoints for assessment and are included in the summaries of these studies. Calculations of blood feeding inhibition were also included for further characterization of the entomological impact of the product.

5.3.1 Tanzania

Study Title (as submitted): Phase II evaluation of deltamethrin Tsara Net long-lasting insecticidal nets compared to DawaPlus® 2.0 against natural populations of *Anopheles arabiensis* in experimental huts and the Ifakara Ambient Chamber Test, Tanzania.

Setting: This multi-faceted study consisted of a traditional experimental hut trial conducted in accordance with current WHO requirements, laboratory based cone bioassays (before and after the experimental hut trial), and a simulated hut study designed by the Ifakara Health Institute of Tanzania (referred to as the Ifakara Ambient Chamber Test (IAC)). All components of the study were conducted in Tanzania from August to September of 2018. First, the experimental hut trial and cone assays were conducted at an Ifakara field branch in the Lupira village of the Ulanga district. Thereafter, the IAC test was conducted at the Ifakara field station in Bagamoyo using the same samples of bednets used in the experimental hut trial.

Treatment Arms:

1. Tsara, unwashed: 120D deltamethrin incorporated polyethylene bednet with a target dose of 2.5 g ai/kg;
2. Tsara, 20x washed (3-day interval between washes)
3. Tsara Soft (DawaPlus 2.0), unwashed: 100D deltamethrin coated polyester bednet with a target dose of 2.0 g ai/kg. This treatment served as the positive control.
4. Tsara Soft (DawaPlus 2.0), 20x washed (3-day interval between washes). This treatment served as the positive control.
5. Untreated polyethylene bednet: this treatment served as the negative control.

Chemical Analysis of Samples:

Product	Condition	AI Content (g/kg)	Calculated % AI Retention Per Wash	Batch Size x Sample
Tsara	Unwashed	2.53 (2.50-2.55)		3x5
	20x washed	1.90 (1.88-1.92)	98.6	3x5
Tsara Soft (DawaPlus 2.0)	Unwashed	1.93 (1.91-1.95)		3x5
	20x washed	0.55 (0.53-0.57)	93.9	3x5

No statistically significant differences between results of different products

5.3.1.1 Ulanga Experimental Hut Trial

Methodology: Susceptibility testing of wild vectors in Ulanga determined that local *Anopheles arabiensis* comprised 99% of the wild *Anopheles* complex and exhibited pyrethroid resistance. The experimental hut trial was carried out over 25 nights with two 5x5 Latin Squares run in parallel using ten unwashed and ten 20x washed bednets per treatment arm. Mosquitoes were collected each morning from within bednets and from inside the huts (walls, ceiling and floors) using mouth aspirators, then sorted and

recorded by treatment. Outcomes measured were percent blood feeding inhibition and 24-hr mortality (M24). M24 was corrected for control mortality.

Bednet samples were sent to the International Institute of Biotechnology and Toxicology (IIBAT) in India for chemical analysis.

Results: Mortality and blood feeding inhibition of free-flying *Anopheles* in Ulanga were low. These results were expected due to the high pyrethroid resistance of the local population. No statistically significant difference was evident between the results obtained in the Tsara Soft and Tsara treatment arms (see Table 6).

Table 6. Mortality and Feeding Inhibition of Free-Flying Pyrethroid Resistant <i>An. arabiensis</i> in a Hut trial				
Product	Condition	% M24	% Feeding Inhibition	Sample Size
Tsara	Unwashed	5.3	49.3	2167
	20x washed	5.6	33.5	2775
Tsara Soft (DawaPlus 2.0)	Unwashed	4.6	47.3	1904
	20x washed	3.8	27.4	2581

No statistically significant differences between results of different products

5.3.1.2 *Cone Bioassays*

Methodology: At the IHI, cone bioassays were conducted on two 20x washed and two unwashed bednets per product, following WHO guidelines and utilizing the Ifakara susceptible *Anopheles gambiae* strain. Outcomes measured were knockdown (kd60) and 24-hr mortality (M24); the latter was corrected for control mortality. The testing was conducted before the hut trial started and after the hut trial was terminated.

Results: The M24 and kd60 for unwashed Tsara and Tsara Soft bednets, before and after the experimental hut trial, were greater than 99%. The M24 for 20x washed samples before the experimental hut trial began was 24.7% for Tsara Soft and 53.6% for Tsara. The pre-trial kd60 for both products (20x washed) was >98%. After the trial, the M24 for 20x washed increased 2-fold for both products and the kd60 was 100% (see Table 7).

Table 7. Mortality and Knockdown of a Susceptible Lab Strain Using the Cone Bioassay							
Product	Outcome	% M24		% kd60		Sample Size	
		Before ¹	After ²	Before ¹	After ²	Before ¹	After ²
Tsara	Unwashed	100	100	100	100	300	200
	20x washed	53.6 ^b (46.2-62.3)	99.4 ^b (98.3-100)	100	100	300	200
Tsara Soft (DawaPlus 2.0)	Unwashed	99.7	100	99.3	100	298	200
	20x washed	24.7 ^a (19.2-30.2)	54.6 ^a (44.0-67.8)	98.9	100	300	200

¹ Testing occurred before the hut trial started

² Testing occurred after the hut trial was terminated

5.3.1.3 *Ifakara Ambient Chamber Test (IACT)*

The IACT is a recently developed, non-standardized method for investigating efficacy of vector control products. The results have been included in this summary for informational purposes only.

Methodology: The chamber is constructed of steel tubes and is 50 m long, 3 m wide, and 2.1 m high, and is covered by UV resistant polyurethane coated netting. The chamber is divided into 10 subsections containing treated bednets. Several mosquito strains can be released simultaneously into each of the subsections with the help of color coding (dusted). This method allows for rapid testing with multiple species or populations.

In this particular study, the susceptible Ifakara strain *Anopheles gambiae* and strongly pyrethroid resistant *Anopheles arabiensis* (Kingani) strain were released into the chambers.

The study design was carried out with two 4x2 Latin Squares run in parallel for eleven nights and using eight unwashed and eight 20x washed bednets per treatment arm (previously used in Ulanga). M24 and feeding inhibition were recorded daily, and reported mortality was corrected for control mortality.

Results:

Susceptible Lab Strain: With 20x washed bednets and using the susceptible *Anopheles gambiae*, no significant difference was detected between control corrected M24 for Tsara and Tsara Soft (99.5% and 88.9% respectively, P-value >0.05). A statistically significant blood feeding inhibition was reported between Tsara (greater inhibition) and Tsara Soft (P-value <0.05) (Results summarized in Table 8).

Resistant Lab Strain: For the resistant *Anopheles arabiensis*, there was a statistically significant M24 observed between 20x washed Tsara (greater mortality) and Tsara Soft treatment arms (P-value <0.05). Likewise, feeding inhibition was greater with washed Tsara than Tsara Soft (P-value <0.05) (Results summarized in Table 8).

Product	Condition	% M24		% Feeding Inhibition		Sample Size	
		S	R	S	R	S	R
Tsara	Unwashed	100	87.9	77.7 ^a	69.5	377	383
	20x washed	99.5	84.9 ^b	84.9 ^b	71.7 ^b	373	384
Tsara Soft (DawaPlus 2.0)	Unwashed	96.7	69.5	77.9 ^a	70.2	385	391
	20x washed	88.9	30.1 ^a	76.0 ^a	28.1 ^a	375	395

Analysis by IIBAT laboratory, India

S = susceptible Ifakara lab strain

R = resistant Ifakara lab strain

WHO Comments:

The study demonstrated that when tested according to the existing standardized methodology, the product Tsara Soft exhibited satisfactory performance against pyrethroid susceptible mosquito strains when considering kd60. Study results indicate that the product should perform as intended to control pyrethroid susceptible mosquitoes over its useful life (20 washes). The additional data generated and reported here may inform product selection decisions based on the scenarios in which the product is intended to be deployed.

5.3.2 Benin

Study Title (as submitted): Phase 2 experimental hut evaluation of the efficacy and wash resistance of Tsara® LN (a pyrethroid-only net by Moon Netting) against pyrethroid resistant *Anopheles gambiae* sl in Cove, Benin

Setting: This study was conducted at the CREC/LSHTM experimental field station in a rice field in Cove, Southern Benin and consisted of three parts: the experimental hut trial, laboratory cone bioassays, and a tunnel test with a mosquito bait. The study was conducted from September to October 2018. The study report is dated November 4, 2018.

Treatment Arms:

1. Negative control, untreated bednet
2. Tsara Soft (DawaPlus 2.0), deltamethrin coated ITN, target dose 2 g/kg, 100 denier – unwashed
3. Tsara Soft (DawaPlus 2.0), deltamethrin coated ITN, target dose 2 g/kg, 100 denier – 20x washed (3-day interval between washes)
4. Tsara deltamethrin bednet, target dose 2.5 g/kg, 120 denier – unwashed
5. Tsara deltamethrin bednet, target dose 2.5 g/kg, 120 denier – 20x washed (3-day interval between washes)

Chemical Analysis of Samples:

Table 9. Chemical Analysis of Samples – Benin Experimental Hut Study				
Product	Condition	AI Content (g/kg)	Calculated % AI Retention Per Wash	Batch Size x Sample
Tsara	Unwashed	2.46		1x5
	20x washed	1.91	98.7	1x5
Tsara Soft (DawaPlus 2.0)	Unwashed	1.95		1x5
	20x washed	0.59	94.2	1x5

No statistically significant differences between results of different products

5.3.2.1 *Experimental Hut Trial*

Methodology: The huts were designed based on the West African hut style. They had cement walls and a palm thatched roof. A total of five huts were used in a Latin Square design. The study was conducted over 25 nights (5 nights per rotation week). Each morning during the study mosquitoes were collected from inside the huts and brought to the lab where they were sorted and recorded by treatment. Outcomes measured included blood feeding inhibition and M24; the latter was corrected for control mortality.

Bednet samples were sent to the IIBAT in India for chemical analysis.

Previous susceptibility testing of wild vector populations indicated that local free-flying *Anopheles colluzzi* and *An gambiae* were resistant to pyrethroids (>90% survival). Survival was mediated by a kdr mutation and overexpression of the metabolic enzyme, CYP6P3.

Results: Mortality and blood feeding inhibition of free-flying *Anopheles* were low. These results were expected due to the high pyrethroid resistance of the local population. No significant difference in mortality was observed between the two products when they were washed 20x. Tsara induced significantly higher blood-feeding inhibition than Tsara Soft for both the unwashed and 20x washed treatments (see Table 10).

Table 10. Mortality and Feeding Inhibition of Free-Flying Pyrethroid Resistant <i>An gambiae</i> in a Hut Trial				
Product	Condition	% Mortality	% Feeding Inhibition	Sample Size
Tsara	Unwashed	3.6 ^a	15.8 ^d	28
	20x washed	2.8	28.8 ^b	71
Tsara Soft (DawaPlus 2.0)	Unwashed	8.3 ^b	11.1 ^c	72
	20x washed	2.6	0 ^a	115

Different letters indicate statistically significant differences.

5.3.2.2 *Cone Bioassay*

Methodology: Cone bioassays were conducted at the CREC laboratory facility using their susceptible *An gambiae* (Kisumu) strain with samples cut from the bednets that were sent to IIBAT laboratory for chemical analysis. Unfed mosquitoes aged 2-5 days were exposed to each treatment for 3 minutes; knockdown was recorded after 1-hour, and mortality after a 24-hr holding period.

Results: The M24 results for unwashed Tsara and Tsara Soft were 100% before the trial. For 20x washed products, M24 did not exceed 20% before or after the trial. Similarly, the kd60 exceeded 95% for unwashed Tsara and Tsara Soft samples before the hut trial but did not exceed 40% for 20x washed samples.

Table 11. Mortality and Knockdown of a Susceptible Lab Strain Using the Cone Bioassay				
Product	Outcome	% M24	% kd60	Sample Size

		Before ¹	After ²	Before ¹	After ²	Before ¹	After ²
Tsara	Unwashed	100	80	100	90	200	200
	20x washed	<20	<20	<40	<20	200	200
Tsara Soft (DawaPlus 2.0)	Unwashed	100	>95	>95	>95	200	200
	20x washed	<20	10	<10	<20	200	200

The M24 and kd60 results were extracted by WHO from figures in the report.

¹Testing occurred before the hut trial started.

²Testing occurred after the hut trial was terminated.

5.3.2.3 Tunnel Test

Methodology: A tunnel test was conducted using unwashed and 20x washed Tsara and Tsara Soft bednet samples with an unspecified mosquito bait. Susceptible *An gambiae* Kisumu aged 5-8 days were exposed in replicates of 100 mosquitoes (3 tunnel tests per treatment) overnight; mortality was recorded 24 hours after collection. The blood-feeding inhibition was calculated based on numbers of blood fed females in the control and insecticide treatments.

Results: The M24 in the Tsara and Tsara Soft (20x washed and unwashed) treatments exceeded 95%. Feeding inhibition was lower in the Tsara Soft (20x washed) treatment compared to Tsara (20x washed) (P-value <0.05). However, there was no statistically significant difference in % feeding inhibition between the results obtained for unwashed Tsara Soft and Tsara.

Table 12. Mortality and Blood Feeding Inhibition of a Susceptible Lab Strain Using the Tunnel Test				
Product	Outcome	% M24	% Feeding Inhibition	Sample Size
Tsara	Unwashed	100	>95	300
	20x washed	100	>95 ^b	300
Tsara Soft (DawaPlus 2.0)	Unwashed	100	>95	300
	20x washed	95	77 ^a	300

WHO Comments:

The study demonstrated that when tested according to the existing standardized methodology, the product Tsara Soft exhibited satisfactory performance against pyrethroid susceptible mosquito strains when considering M24. In situations where cone test efficacy results do not reach the thresholds for M24 or kd60, the guidelines provide the option to conduct the tunnel test to investigate the efficacy with a bait and allowing for more realistic mosquito behavior to take place. The results of the study indicate that the product should perform as intended to control pyrethroid susceptible mosquitoes over its useful life (20 washes). The additional data generated and reported here may inform product selection decisions based on the scenarios in which the product is intended to be deployed.

5.3.3 Burkina Faso

Study Title (as submitted): Phase II field evaluation of long-lasting nets DawaPlus 3.0 (deltamethrin and PBO in roof panel; deltamethrin alone in the side panels) and DawaPlus 4.0 (deltamethrin and PBO) of Tana Netting against natural populations of *Anopheles gambiae* sl in Burkina Faso

Setting: This study was carried out at the field station in a rice field in Vallée du Kou in Burkina Faso August to October 2016. The study was designed to assess the efficacy of DawaPlus 3.0 and DawaPlus 4.0 against pyrethroid resistant mosquitoes under semi-field conditions. Tsara Soft (DawaPlus 2.0) was used as the positive control in the trial. The submitted report is a draft version dated January 21, 2017.

This study consisted of several parts:

- An experimental hut trial using free-flying local mosquito populations as the positive control.
- An *in-situ* cone bioassay using a susceptible lab strain as well as the local vector was conducted on bednets hanging in the experimental huts.
- A laboratory cone bioassay using a susceptible lab strain.
- A laboratory tunnel test using a susceptible lab strain.

Treatment Arms:

1. Untreated polyethylene bednet – negative control
2. Tsara Soft (DawaPlus 2.0), deltamethrin incorporated (80 mg/m²), positive control – unwashed
3. Tsara Soft (DawaPlus 2.0), deltamethrin incorporated (80 mg/m²), positive control – 20x washed (1-day interval between washes)
4. DawaPlus 3.0 – unwashed
5. DawaPlus 3.0 – 20x washed
6. DawaPlus 4.0 – unwashed
7. DawaPlus 4.0 – 20x washed

For the purpose of this assessment, only those results for Tsara Soft have been considered.

5.3.3.1 Experimental Hut Trial

Methodology: Wild *An coluzzii* were collected as larvae and reared to adults at the insectary of the IRSS laboratory. The experiment was set up as a Latin Square design with 7 treatment arms and 3 replicates each. The duration of the trial was 9 weeks. Control corrected cumulative mortality (dead collected +24-hr mortality) and blood-feeding inhibition were investigated.

Results: The percent cumulative mortality recorded for resistant, free-flying *Anopheles* in Tsara Soft (DawaPlus 2.0) treatment arms was 15%, and 11% in the negative control. There was no statistically significant difference between the two treatment arms.

Likewise, blood-feeding inhibition for resistant, free-flying *Anopheles* exposed to Tsara Soft (DawaPlus 2.0) (unwashed and 20x washed) did not differ from the negative, non-treated control.

5.3.3.2 Cone Bioassay

Methodology: Laboratory reared, susceptible *Anopheles gambiae* (Kisumu) as well as local pyrethroid resistant vectors were tested in cone bioassays on washed and unwashed ITN products *in-situ* (before and after the hut trial), and in the laboratory after the experimental hut trial. Outcomes measured were M24 and kd60.

Results:

In-Situ Test: The cone bioassay results conducted on the unwashed and 20x washed ITNs before and after the hut trial resulted in 100% M24 of the susceptible Kisumu strain and >95% kd60. The number of mosquitoes tested was not reported.

The M24 results for the local, resistant *Anopheles* vector was <5% on washed and unwashed Tsara Soft treatments (corrected for control mortality). There was no statistically significant difference between the results obtained from unwashed and 20x washed treatments. The number of mosquitoes tested was not reported.

Laboratory test. When the cone bioassay was repeated in the lab, the Tsara Soft results for the susceptible Kisumu strain were reflective of the *in-situ* cone bioassays. Mortality ranged from 92-100%, while knockdown was above 95% for both unwashed and 20x washed Tsara Soft bednet samples (between 102-131 mosquitoes tested per replicate).

The M24 for the local, resistant vector when tested in the lab was less <5%. There was no difference between mortalities observed on unwashed and 20x washed Tsara Soft bednet samples (between 103-117 mosquitoes tested per replicate).

5.3.3.3 Tunnel Test

Methodology: Laboratory reared, susceptible *Anopheles gambiae* (Kisumu) and the local pyrethroid resistant vector were tested using unwashed and 20x washed samples of the tested products. The WHO guidelines were observed in conducting the test. The outcomes measured were M24 (control corrected) and blood feeding. Blood-feeding inhibition was thereafter calculated.

Results:

Susceptible Lab Strain: The M24 for the susceptible Kisumu strain was greater than 90% for both unwashed and 20x washed Tsara Soft samples. The number of mosquitoes tested was not reported. Blood feeding inhibition was >90% for unwashed and 20x washed Tsara Soft treatments.

Local, Resistant Strain: The M24 of the local resistant *Anopheles* vector was less than 50% for unwashed and 20x washed Tsara Soft. There was no significant difference between the unwashed and 20x washed treatments (see Table 13).

Blood-feeding inhibition for the local resistant vector was <40% for unwashed and 80% for 20x washed Tsara Soft treatments.

Table 13. Mortality and Blood-Feeding Inhibition of Susceptible (Kisumu) and Resistant <i>Anopheles</i> (Local Vector) Using the Tunnel Test				
	Product	Outcome	% M24*	% blood-feeding inhibition
Susceptible Lab Strain	Tsara Soft (DawaPlus 2.0)	Unwashed	>90	>90
		20x washed	>90	>90
Local Resistant Vector	Tsara Soft (DawaPlus 2.0)	Unwashed	<50	<40
		20x washed	<40	80

*The M24 results were extracted from figures in the report and are approximations.

WHO Comments:

The study demonstrated that the product Tsara Soft, when tested according to the existing standardized methodology, exhibited satisfactory performance against pyrethroid susceptible mosquito strains when considering M24 and kd60. The results of the study indicate that the product should perform as intended to control pyrethroid susceptible mosquitoes over its useful life (20 washes). The additional data generated and reported here may inform product selection decisions based on the scenarios in which the product is intended to be deployed.

5.4 Summary of Field studies

The long-term field studies conducted for the product Tsara Soft were initiated in 2014. At the time of initiation of these studies, the product was referred to by its previous name and owner, DawaPlus 2.0, Tana Netting FZE.

5.4.1 Burkina Faso

Study Title (as submitted): Comparative efficacy of long-lasting insecticidal net DawaPlus[®] 2.0 vs [Positive Control] in Burkina Faso

Setting:

Two Health Districts, called 15 and 22 of Bobo-Dioulasso region in Western Burkina Faso;

Start date: August 2014

End date: July 2017

Treatment Arms:

1. DawaPlus[®] 2.0, deltamethrin (2.0 g/kg; target dose 80 mg/m²)
2. Positive Control: Prequalified pyrethroid coated polyethylene bednet

Experimental design:

This long-term field study was designed in accordance with the current WHO testing guidelines for insecticide treated bednets. The two products were distributed free of cost to an equal number of households. Randomization took place at household level. Follow-up surveys were performed after

distribution of nets, and at each survey a randomized sample of thirty nets was collected per arm for the purpose of bioefficacy and chemical content analysis.

5.4.1.1 *Cone Bioassay*

Methodology: The standard WHO cone test was used to investigate mortality and knockdown in order to understand the residual efficacy for each type of net using the lab susceptible *An. gambiae* s.s. Kisumu strain.

Results: For Tsara Soft, the average kd60 was >95% and the M24 was >99% through 36 months. The range of KD60 and mortality at 24h is presented in Table 14.

Table 14. Cone test results for DawaPlus®2.0 and Positive Control conducted with pyrethroid susceptible <i>Anopheles gambiae</i> s.s. (Kisumu Strain)						
	Tsara Soft			Positive Control		
Survey month	No. nets	Mean KD60	Mean 24-hour mortality	No. nets	Mean KD60	Mean 24-hour mortality
0	30	98.6% [98.07- 99.2]	99.7% [99.5- 99.9]	30	99.58% [99.22- 99.94]	100
6	30	96.88% [95.3- 97.5]	100	30	97.98% [96.83- 98.3]	100
12	30	95.9% [94.25- 97.5]	100	30	96.91 [96.73- 98.10]	100
18	30	96.37 [93.5- 99.23]	99.8 [99.57- 100]	30	99.73 [99.48- 99.99]	100
24	30	97.7 [95.36- 100]	99.87 [99.59- 100]	30	99.33 [98.49- 100]	99.93 [99.8-100]
30	30	99.73 [99.34 -100]	100	30	99.63 [99.20-100]	100
36	50	99.92 [99.81- 100]	100	50	99.96 [99.88-100]	100

5.4.1.2 *Residual Chemical Content*

Methodology: Samples of the two products were subjected to chemical analysis at the beginning of the trial (t₀) to ensure that the target dose of deltamethrin was correct. Samples were all analyzed at yearly intervals (t₁₂, 24 and 36) to facilitate interpretation of bioassay data. The amount of deltamethrin was estimated using HPLC according to the appropriate established method.

Results: The initial concentration of deltamethrin in Tsara Soft was within the acceptable margin of variation of the manufacturer’s specification at the beginning of the field trial. Over time the deltamethrin content decreased with household use. Tsara Soft and the positive control performed similarly. For Tsara Soft, the average cumulative deltamethrin loss was 50% (12 months), 68% (24

months), and 73% (36 months). The same trend was observed for the positive control for which there was a 75% loss of AI after 36 months.

WHO Comments:

The study demonstrated that, when tested according to the existing standardized methodology, the product Tsara Soft exhibited satisfactory performance against pyrethroid susceptible mosquito strains in 100% of samples taken, when considering M24 and kd60 over a period of 3 years. The results of the study indicate that the product should perform as intended to control pyrethroid susceptible mosquitoes over its intended useful life (3 years).

5.4.2 Indonesia

Study Title (as submitted): Comparative efficacy of long-lasting insecticidal net (Tsara Soft 100D vs. Tsara Soft 150D) in Indonesia

Setting:

Southwest Sumba District, East Nusa Tenggara Province, Indonesia

Start date: Sept 2015

End date: Sept 2018

Treatment Arms:

1. Tsara Soft 100D, deltamethrin (2.0 g/kg; target dose 80 mg/m²) on a 100-denier yarn
2. Tsara Soft 150D deltamethrin (2.0 g/kg; target dose 80 mg/m²) on a 150-denier yarn

Experimental design:

The study design was an open label household randomized prospective longitudinal cohort study of Tsara Soft 100D and 150D versions. The target number of households was approximately 100 (300 nets) per arm. A process was implemented to ensure a household randomization and net distribution.

A sampling scheme was devised to collect nets during the 3-year study. Five nets of each type were sampled at baseline and after 6 months, and ten nets of each type at 12, 24 and 36 months. From each of the sampled nets, four pieces of 30 cm x 30 cm size were cut from positions 1 to 5 for cone bioassays and a further piece was cut adjacent to the bioefficacy assay samples for chemical assessment.

5.4.2.1 Cone Bioassay

Methodology: The standard WHO cone test was used to investigate mortality and knockdown in order to understand the residual efficacy for each type of net using the lab fully pyrethroid susceptible *Anopheles aconitus*.

Results: Knockdown and mortality exceeded 85% and 95%, respectively, for both versions of Tsara Soft at the six time points. The range of KD60 and mortality at 24h is presented in Table 15.

Table 15. Cone test results for Tsara Soft conducted with pyrethroid susceptible <i>Anopheles aconitus</i>						
	Tsara Soft 100D			Tsara Soft 150D		
Survey month	No. nets	Mean KD60	Mean 24-hour mortality	No. nets	Mean KD60	Mean 24-hour mortality
0	4	93.6 (90.73 – 96.47)	100	5	92.48 (89.68 – 95.28)	100
6	5	98.7 (97.67 – 99.72)	100	5	99.12 (98.12 – 100.12)	100
12	10	99.20 (98.65 – 99.75)	100	10	99.40 (98.92 – 99.88)	100
18	10	88.60 (85.46 – 91.74)	96.7 (95.17 – 98.23)	10	91.36 (88.85 – 93.86)	98.61 (97.61 – 99.62)
24	10	93.10 (90.89 – 95.30)	100	10	99.37 (98.87 – 99.87)	98.85 (98.01 – 99.69)
30	10	98.85 (98.07 – 99.64)	100	10	91.69 (89.05 – 94.33)	99.48 (98.88 – 100.09)
36	10	100	100	10	100	100
Total	59	95.95 (95.20 – 96.70)	99.43 (99.16 – 99.70)	60	96.11 (95.39 – 96.82)	99.48 (99.24 – 99.73)

5.4.2.2 Residual Chemical Content

Methodology: Samples of the two products were subjected to chemical analysis at the beginning of the trial (t₀) to ensure that the target dose of deltamethrin was correct. Samples were all analyzed at yearly intervals (t₁₂, 24 and 36) to facilitate interpretation of bioassay data. The amount of deltamethrin was estimated using HPLC according to the appropriate established method.

Results: The initial concentration of deltamethrin in Tsara Soft was within the acceptable margin of variation of the manufacturer’s specifications at the beginning of the field trial. Over time the deltamethrin content decreased with household use. The 100D and 150D versions of Tsara Soft performed similarly, and the deltamethrin loss was reported as 55% (both versions) after year 1, 69% (100D) vs. 55% (150D) after year 2, and 77% (100D) vs. 68% (150D) of the original dose after year 3.

WHO Comments:

The study demonstrated that the product Tsara Soft, when tested according to the existing standardized methodology, exhibited satisfactory performance against pyrethroid susceptible mosquito strains in >80% of samples when considering M24 and kd60 over a period of 3 years. The results of the study indicate that the product should perform as intended to control pyrethroid susceptible mosquitoes over its useful life (3 years).

5.4.3 Tanzania

Study Title (as submitted): Comparative efficacy of long-lasting insecticidal net DawaPlus[®] 2.0 vs [Positive Control] in Tanzania

Setting:

Mbingu village in the Kilombero valley (8.21 °S and 36.24 °E), south-west Tanzania

Start date: July 2014

End date: July 2017

Treatment Arms:

1. DawaPlus[®] 2.0, deltamethrin (2.0 g/kg; target dose 80 mg/m²)
2. Positive Control: Prequalified pyrethroid coated polyethylene bednet

Experimental design:

This long-term field study was designed in accordance with the current WHO testing guidelines for insecticide treated bednets. The study was a double blinded household randomized prospective longitudinal study, designed to investigate the performance of Tsara Soft and a positive control. The two products were distributed free of cost to an equal number of households (>430 households and 1830 nets per arm). Randomization took place at household level. Follow-up surveys were performed after distribution of nets, and at each survey a randomized sample of 30 nets was collected per arm at 6, 12, 18 and 24 months, and 50 nets of each type at 36 months. Collected nets were submitted to cone bioassays and chemical content analysis plus a physical integrity test.

5.4.3.1 Cone Bioassay

Methodology: The standard WHO cone test was used to investigate mortality and knockdown in order to understand the residual efficacy for each type of net using the lab susceptible *An. gambiae* s.s. Ifakara strain.

Results: For both Tsara Soft and the positive control treatments, the average kd60 was >98% following six months of use. The kd60 then oscillated between 93% and 100% over time for both products. Overall, the kd60 decreased slightly from the beginning to the end of the study. A reduction of M24 was also observed from baseline to 36 months with the lowest measured value for Tsara Soft being 86.9% at 30 months. Overall, for Tsara Soft, M24 was >80% throughout the study.

Table 16. Cone test results for Tsara Soft and positive control conducted with pyrethroid susceptible *Anopheles gambiae* (Ifakara Strain)

Survey month	Tsara Soft			Positive Control		
	No. nets	Mean KD60	Mean 24-hour mortality	No. nets	Mean KD60	Mean 24-hour mortality
6	29	98.1% (97.6-98.6)	97.8% (97.1-98.5)	28	99.2% (98.8-99.6)	98.7% (98.1-99.2)
12	30	93.2% (92.0-94.3)	93.1% (91.9-94.2)	30	99.7% (99.4 – 99.9)	97.3% (96.5-98.1)
18	30	100%	92.5% (90.9-94.1)	30	100%	79.9% (77.4-82.5)
24	30	99.5% (99.1-99.8)	87.4% (85.3-89.4)	30	98.8% (98.2-99.5)	83.0% (80.4-85.7)
30	30	93.9% (92.3-95.6)	86.9% (84.6-89.1)	30	93.3% (92.0-94.7)	80.2% (77.3-83.1)
36	50	94.2% (93.3-95.0)	96.2% (95.5-96.9)	50	95.5% (94.7-96.3)	95.2% (94.2-96.1)
Total	199	96.6% (95.7-97.2)	92.3% (90.9-93.7)	198	97.8% (97.2-98.3)	89.1% (87.3-90.8)

5.4.3.2 *Residual Chemical Content*

Methodology: Chemical analysis was performed by measuring the deltamethrin content in each net type following the method of High Performance Liquid Chromatography with UV Diode Array Detection (HPLC-DAD).

Results: The initial concentration of deltamethrin in Tsara Soft and the positive control were within the acceptable margin of variation of the manufacturer’s specification at the beginning of the field trial. After one year and two years of household use the mean deltamethrin content decreases for both nets with a similar trend. The deltamethrin loss for Tsara Soft was reported as 53% after year 1 and 79% after years 2 and 3. The same trend was observed for the positive control with loss of insecticide content of 63% after year 1, 80% after year 2, and 82% after year 3.

WHO Comments:

The study demonstrated that the product Tsara Soft, when tested according to the existing standardized methodology, exhibited satisfactory performance against pyrethroid susceptible mosquito strains when considering M24 and kd60 over a period of 3 years. The mean kd60 and/or M24 were above the target thresholds (i.e. ≥95% mosquito knockdown rate or ≥80% mortality) with a standard WHO cone bioassay at all timepoints. The percentage of bednets sampled which met the threshold was variable and decreased between 24 (100%) and 30 months (73%) and then increased to 94% at the 36 months. This variability could be influenced by the low sample size of nets (n =30) at each time point. The same trend was also seen for the positive control supporting the interpretation that this trend could be an artifact of sample size or testing.

5.5 Efficacy Conclusions

Considering the entirety of the submitted efficacy studies in lab, semi-field, and field settings, there is sufficient evidence to demonstrate that Tsara Soft meets the efficacy requirements for prequalification.

6 Labelling

The proposed Declaration of Labelling has been reviewed by PQT/VCP and found to be consistent with the supporting information.

7 Post-Prequalification Commitments

7.1 Monitoring of Product Compliance

The applicant, NRS Moon Netting FZ, will be responsible for submitting quarterly reports for a period of two years to WHO PQT/VCP confirming the adherence to the declared formulation and manufacturing process at all manufacturing sites. These quarterly reports must contain the following:

- Affirmation that the manufacturing of products has been conducted in accordance with the declared product formulation and manufacturing process.
- List of production batches including the batch ID and production date
- Supporting QA/QC reports verifying post-production compliance with the established specification

The quarterly reports must be submitted on or before the following dates:

- 31 December 2020
- 31 March 2021
- 30 June 2021
- 30 September 2021
- 31 December 2021
- 31 March 2022
- 30 June 2022
- 30 September 2022
- 31 December 2022

WHO PQ may extend this period for required reporting based on the review of submitted reports and/or complaints.

8 Pre-Qualification Listing Decision

The review of the dossier submitted for the product Tsara Soft has been completed by PQT/VCP. The results of the assessments show the product is safe and effective when produced according to the declared formulation and used according to the directions for use on the label. The product is allowed inclusion on the list of prequalified vector control products.

9 References

- Quality
 1. 2018. Tsara Soft Product Dossier submitted to WHO
- Safety – See Appendix C
- Efficacy
 1. Bayili, K., H. Ki, B. Sow, B. Bahili, A. Ouattara, R. K. Dabire, and A. Diabate. 2018. WHO Phase 1 laboratory evaluation of the efficacy and wash resistance of Tsara LN a pyrethroid-only LLIN manufactured by NRS Moon Netting FZE. IRSS, Benin.
 2. Ngufor, Corine (2017) Regeneration time, wash resistance and efficacy of long lasting insecticidal mosquito nets Royal Guard® of Disease Control Technologies, USA against susceptible and resistant strains of *Anopheles gambiae*, Cove, Benin - CREC/LSHTM Collaborative Research Programme, Centre de Recherche Entomologique de Cotonou (CREC), Benin
 3. Moore, Sarah (2018). Phase II Evaluation of alpha-cypermethrin and pyriproxyfen Royal Guard 120D long-lasting insecticidal nets compared to positive control against natural populations of *An. arabiensis* in experimental huts, Tanzania – Ifakara Health Institute, Bagamoyo, Tanzania
 4. Moore, Sarah (2018). Phase II evaluation of Tsara long lasting insecticidal nets compared to DawaPlus 2.0 against natural populations of *Anopheles sp.* In the experimental huts, Indonesia – Eijkman Institute, SW Sumba District, Jakarta, Indonesia
 5. Ngufor, Corine (2018). Phase II Experimental Hut Evaluation of The Efficacy and Wash Resistance of Royal Guard Against Wild Pyrethroid Resistant *Anopheles gambiae* sl in Cove, Benin - CREC/LSHTM Collaborative Research Programme, Centre de Recherche Entomologique de Cotonou (CREC), Benin

Appendix A: Confidential Business Information

Appendix B: Complete Physical/Chemical Data Submitted

Table 17. Chemical & Physical Properties – Tsara Soft			
Title	Study Number	Test method ID	Result
Active ingredient content in Tsara Soft LLIN 75 denier-2.7 g/kg LN samples (3 batches, 75D_A; 75D_B; 75D_C 6 samples from each batch were tested)	IIBAT Study No.:19095 Determination of deltamethrin content in Tsara Soft (75D-2.7g/kg, 100D-2.0g/kg, 150D-2.0g/kg) long lasting (coated onto polyester) insecticidal net	CIPAC M 333/LN/M/(3)	The deltamethrin content in 75 denier samples ranges from 2.62 to 2.78 g/kg. Specification value: 2.7 g/kg Acceptable range for deltamethrin content is 2.025 to 3.375 g/kg; all results were within the acceptable range R-isomer content is in the range 0.03-0.04 g/kg *Note 1.
Active ingredient content in Tsara Soft LLIN 100 denier-2.0 g/kg LN samples (5 batches, 100D_A; 100D_B; 100D_C; 100D_D; 100D_E 6 samples from each batch were tested)	IIBAT Study No.:19095 Determination of deltamethrin content in Tsara Soft (75D-2.7g/kg, 100D-2.0g/kg, 150D-2.0g/kg) long lasting (coated onto polyester) insecticidal net	CIPAC M 333/LN/M/(3)	The deltamethrin content in 100 denier samples ranges from 2.27 to 2.37 g/kg. Specification value: 2.0 g/kg Acceptable range for deltamethrin content is 1.5 to 2.5 g/kg; all results were within the acceptable range R-isomer content is in the range 0.02-0.03 g/kg *Note 1.
Active ingredient content in Tsara Soft LLIN 150 denier-2.0 g/kg LN samples (3 batches, 150D_A; 150D_B; 150D_C; 6 samples from each batch were tested)	IIBAT Study No.:19095 Determination of deltamethrin content in Tsara Soft (75D-2.7g/kg, 100D-2.0g/kg, 150D-2.0g/kg) long lasting (coated onto polyester) insecticidal net	CIPAC M 333/LN/M/(3)	The deltamethrin content in 150 denier samples ranges from 1.81 to 1.91 g/kg. Specification value: 2.0 g/kg Acceptable range for deltamethrin content is 1.5 to 2.5 g/kg; all results were within the acceptable range R-isomer content is in the range 0.02-0.04 g/kg *Note 1.
Storage stability, active ingredient content in Tsara Soft LLIN 75 denier before and after elevated temperature exposure (14 days at 54 ± 2 °C) (1 batch, 5 pieces were tested)	IIBAT Study No.:19094 Physical-Chemical Analysis of Tsara Soft (Deltamethrin 2.7g/kg-White) Long Lasting (coated onto polyester) insecticidal net-75 Denier Yarn	CIPAC MT 46.3.4	deltamethrin content of unexposed LLIN (average of five pieces) : 2.71 g/kg deltamethrin R-isomer content: 0.04 g/kg *Note 2. deltamethrin content of exposed LLIN (average of five pieces) : 2.66 g/kg deltamethrin R-isomer content: 0.04 g/kg Percentage of active ingredient present in the net after 14 days at 54 ± 2°C : 98.2%
Storage stability, active ingredient content in Tsara Soft LLIN 100 denier before and after elevated temperature exposure (14 days at 54 ± 2 °C) (1 batch, 5 pieces were tested)	IIBAT Study No.:19093 Physical-Chemical Analysis of Tsara Soft (Deltamethrin 2g/kg-Blue) Long Lasting (coated onto polyester) insecticidal net-100 Denier Yarn	CIPAC MT 46.3.4	deltamethrin content of unexposed LLIN (average of five pieces) : 2.27 g/kg deltamethrin R-isomer content: 0.03 g/kg *Note 2 deltamethrin content of exposed LLIN (average of five pieces) : 2.20 g/kg deltamethrin R-isomer content: 0.04 g/kg Percentage of active ingredient present in the net after 14 days at 54 ± 2°C : 96.9%
Storage stability, active ingredient content in Tsara Soft LLIN 150 denier before and after elevated	IIBAT Study No.:19087 Physical-Chemical Analysis of Tsara Soft	CIPAC MT 46.3.4	deltamethrin content of unexposed LLIN (average of five pieces) : 1.83 g/kg deltamethrin R-isomer content: 0.03 g/kg *Note 2

Table 17. Chemical & Physical Properties – Tsara Soft

Title	Study Number	Test method ID	Result
temperature exposure (14 days at 54 ± 2 °C) (1 batch, 5 pieces were tested)	(Deltamethrin 2g/kg-White) Long Lasting (coated onto polyester) insecticidal net-150 Denier Yarn		deltamethrin content of exposed LLIN (average of five pieces) : 1,79 g/kg deltamethrin R-isomer content: 0.03 g/kg Percentage of active ingredient present in the net after 14 days at 54 ± 2°C : 97.8%
Wash resistance index (after 4 washing, 1batch, 3 pieces) before and after elevated temperature exposure (14 days at 54 ± 2 °C) 75 Denier Yarn	IIBAT Study No.:19094 Physical-Chemical Analysis of Tsara Soft (Deltamethrin 2.7g/kg-White) Long Lasting (coated onto polyester) insecticidal net-75 Denier Yarn	CIPAC MT195	Average wash resistance index: for unexposed LLIN: 98.4% for exposed LLIN: 98.8% Acceptable range: 90-100%
Wash resistance index (after 4 washing, 1batch, 3 pieces) before and after elevated temperature exposure (14 days at 54 ± 2 °C) 100 Denier Yarn	IIBAT Study No.:19093 Physical-Chemical Analysis of Tsara Soft (Deltamethrin 2g/kg-Blue) Long Lasting (coated onto polyester) insecticidal net-100 Denier Yarn	CIPAC MT195	Average wash resistance index: for unexposed LLIN: 98.5% for exposed LLIN: 99.3% Acceptable range: 90-100%
Wash resistance index (after 4 washing, 1batch, 3 pieces) before and after elevated temperature exposure (14 days at 54 ± 2 °C) 150 Denier Yarn	IIBAT Study No.:19087 Physical-Chemical Analysis of Tsara Soft (Deltamethrin 2g/kg-White) Long Lasting (coated onto polyester) insecticidal net-150 Denier Yarn	CIPAC MT195	Average wash resistance index: for unexposed LLIN: 98.2% for exposed LLIN: 98.5% Acceptable range: 90-100%
Mass per unit area (1batch,5pieces) 75 Denier Yarn	IIBAT Study No.:19094 Physical-Chemical Analysis of Tsara Soft (Deltamethrin 2.7g/kg-White) Long Lasting (coated onto polyester) insecticidal net-75 Denier Yarn	ISO 3801/EN 12127	Average weight: 31.91 g/m ² Acceptable value: 30 g/m ² ± 10%
Mass per unit area (1batch,5pieces) 100 Denier Yarn	IIBAT Study No.:19093 Physical-Chemical Analysis of Tsara Soft (Deltamethrin 2g/kg-Blue) Long Lasting (coated onto polyester) insecticidal net-100 Denier Yarn	ISO 3801/EN 12127	Average weight: 39.49 g/m ² Acceptable value: 40 g/m ² ± 10%
Mass per unit area (1batch,5pieces) 150 Denier Yarn	IIBAT Study No.:19087 Physical-Chemical Analysis of Tsara Soft (Deltamethrin 2g/kg-White) Long Lasting	ISO 3801/EN 12127	Average weight: 45.96 g/m ² Acceptable value: 42 g/m ² ± 10%

Table 17. Chemical & Physical Properties – Tsara Soft

Title	Study Number	Test method ID	Result
	(coated onto polyester) insecticidal net-150 Denier Yarn		
Mesh size (1 batch, 5 pieces) 75 Denier Yarn	IIBAT Study No.:19094 Physical-Chemical Analysis of Tsara Soft (Deltamethrin 2.7g/kg-White) Long Lasting (coated onto polyester) insecticidal net-75 Denier Yarn	WHO Specification 333/LN/2	Average mesh size: 24 holes/cm ² Acceptable value: average shall be not less than 24 holes/cm ² and the lowest value shall be not less than 23 holes/ cm ²
Mesh size (1 batch, 5 pieces) 100 Denier Yarn	IIBAT Study No.:19093 Physical-Chemical Analysis of Tsara Soft (Deltamethrin 2g/kg- Blue) Long Lasting (coated onto polyester) insecticidal net-100 Denier Yarn	WHO Specification 333/LN/2	Average mesh size: 24 holes/cm ² Acceptable value: average shall be not less than 24 holes/cm ² and the lowest value shall be not less than 23 holes/ cm ²
Mesh size (1 batch, 5 pieces) 150 Denier Yarn	IIBAT Study No.:19087 Physical-Chemical Analysis of Tsara Soft (Deltamethrin 2g/kg- White) Long Lasting (coated onto polyester) insecticidal net-150 Denier Yarn	WHO Specification 333/LN/2	Average mesh size: 14 holes/cm ² Acceptable value: average shall be not less than 14 holes/cm ² and the lowest value shall be not less than 13 holes/ cm ²
Dimensional stability before and after elevated temperature exposure (14 days at 54 ± 2 °C) 1 batch, 2 samples 75 Denier Yarn	IIBAT Study No.:19094 Physical-Chemical Analysis of Tsara Soft (Deltamethrin 2.7g/kg-White) Long Lasting (coated onto polyester) insecticidal net-75 Denier Yarn	WHO Specification 333/LN/2	before storage stability test: -1.0% warp and -1.2% weft after storage stability test: -1.3% warp and -1.5% weft Acceptable value: not more than 10% shrinkage and not more than 5% expansion in both directions
Dimensional stability before and after elevated temperature exposure (14 days at 54 ± 2 °C) 1 batch, 2 samples 100 Denier Yarn	IIBAT Study No.:19093 Physical-Chemical Analysis of Tsara Soft (Deltamethrin 2g/kg- Blue) Long Lasting (coated onto polyester) insecticidal net-100 Denier Yarn	WHO Specification 333/LN/2	before storage stability test: -1.0% warp and -1.0% weft after storage stability test: -1.3% warp and -1.5% weft Acceptable value: not more than 10% shrinkage and not more than 5% expansion in both directions
Dimensional stability before and after elevated temperature exposure (14 days at 54 ± 2 °C) 1 batch, 2 samples 150 Denier Yarn	IIBAT Study No.:19087 Physical-Chemical Analysis of Tsara Soft (Deltamethrin 2g/kg- White) Long Lasting (coated onto polyester)	WHO Specification 333/LN/2	before storage stability test: -0.7% warp and -0.8% weft after storage stability test: -1.0% warp and -1.2% weft Acceptable value: not more than 10% shrinkage and not more than 5% expansion in both directions

Table 17. Chemical & Physical Properties – Tsara Soft

Title	Study Number	Test method ID	Result
	insecticidal net-150 Denier Yarn		
Bursting strength of fabric before and after elevated temperature exposure (14 days at 54 ± 2 °C) 1 batch, 3 samples 75 Denier Yarn	IIBAT Study No.:19094 Physical-Chemical Analysis of Tsara Soft (Deltamethrin 2.7g/kg-White) Long Lasting (coated onto polyester) insecticidal net-75 Denier Yarn	ISO 13398-2:1999	Bursting strength: before storage stability test: 345 kPa after storage stability test: 342.5 kPa Acceptable value: min. 250 kPa
Bursting strength of fabric before and after elevated temperature exposure (14 days at 54 ± 2 °C) 1 batch, 3 samples 100 Denier Yarn	IIBAT Study No.:19093 Physical-Chemical Analysis of Tsara Soft (Deltamethrin 2g/kg-Blue) Long Lasting (coated onto polyester) insecticidal net-100 Denier Yarn	ISO 13398-2:1999	Bursting strength: before storage stability test: 437.5 kPa after storage stability test: 438.3 kPa Acceptable value: min. 350 kPa
Bursting strength of fabric before and after elevated temperature exposure (14 days at 54 ± 2 °C) 1 batch, 3 samples 150 Denier Yarn	IIBAT Study No.:19087 Physical-Chemical Analysis of Tsara Soft (Deltamethrin 2g/kg-White) Long Lasting (coated onto polyester) insecticidal net-150 Denier Yarn	ISO 13398-2:1999	Bursting strength: before storage stability test: 521.4 kPa after storage stability test: 515.8 kPa Acceptable value: min. 420 kPa
Flammability 75 Denier Yarn	IIBAT Study No.:19094 Physical-Chemical Analysis of Tsara Soft (Deltamethrin 2.7g/kg-White) Long Lasting (coated onto polyester) insecticidal net-75 Denier Yarn	EN 1102:2016	no ignition, no propagation of the flame
Flammability 100 Denier Yarn	IIBAT Study No.:19093 Physical-Chemical Analysis of Tsara Soft (Deltamethrin 2g/kg-Blue) Long Lasting (coated onto polyester) insecticidal net-100 Denier Yarn	EN 1102:2016	no ignition, no propagation of the flame
Flammability 150 Denier Yarn	IIBAT Study No.:19087 Physical-Chemical Analysis of Tsara Soft (Deltamethrin 2g/kg-White) Long Lasting (coated onto polyester) insecticidal net-150 Denier Yarn	EN 1102:2016	no ignition, no propagation of the flame

Note 1:

- The calibration required for the quantitation of deltamethrin R-isomer was not provided in the IIBAT 19095 study. According to the raw data for the quantitation of deltamethrin R-isomer presented in Table 3., Table 5. and Table 7 of the study, the R-isomer content was calculated based on the deltamethrin calibration point CC (standard deltamethrin weighing in 51.34 mg, purity 994 g/kg) instead of using a calibration point for the R-isomer. In the other three studies (IIBAT 19094; IIBAT 19093 and IIBAT19087) the used R-isomer had a purity of 514.6 g/kg and for the CC concentration around 100 mg was weighed in.

Note 2:

- In studies IIBAT 19095, IIBAT19094, IIBAT 19093, IIBAT19087 the signal values for the deltamethrin R-isomer in the samples are significantly lower than the signal for the calibration points, so the sample signal values are out of the calibration range.

Appendix C: PQ Letter of Suspension for Tsara Soft – 12 December 2019



World Health
Organization

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E-mail :	pqvectorcontrol@who.int	Plot. No MO0659
In reply please refer to :	V2-447-3/ML/DS/1	Street N200/202, Jebel Ali Free Zone Dubai
Your reference:	028-003	Etats Arabes Unis

12 December 2019

Dear Mrs Thorup,

WHO Prequalification Team – Vector Control Vector Control Product Prequalification: Suspension

According to the established procedures for the prequalification of vector control products, the World Health Organization (WHO) reserves the right to terminate this procedure for a specific product if the applicant is not able to provide the required information or implement the corrective actions within a specified time period, or if the information supplied is inadequate to complete this procedure, or when serious safety and/or quality concerns arise.

There is uncertainty regarding the quality and efficacy of the product Tsara Soft (PQ Ref # 028-003) also known as DawaPlus 2.0, and it cannot be determined that the data submitted to WHO to support the World Health Organization Pesticides Evaluation Scheme (WHOPEs) recommendation of the product and subsequent conversion to a prequalification listing, is still applicable to the current product as formulated and manufactured. In addition, given the relationship between quality and efficacy, the multiple Post PQ Change (PPQC) applications submitted and other information provided in response to investigation of complaints cannot be reviewed in isolation, but must be integrated in a complete review of the product. Taking this information in consideration, it has been determined that the NRS Moon Netting, the responsible manufacturer for the current product Tsara Soft, would need to submit a full data package to support a prequalification listing for Tsara Soft. A complete dossier was submitted on 9 December 2019 and the assessment of this submission has been initiated.

The process for conversion from WHOPEs recommendations to prequalification was based on confirmation that products were supported by existing WHOPEs recommendations by ensuring availability of previous quality, safety and efficacy reviews. The documentation of the conversion process identified that further review and requests for additional data may be required for converted products based on factors which included product concerns (complaints/failure reports) and/or changes to the product.

A series of complaints have been received regarding product failures (Out of Specification findings) and mis-production of the product DawaPlus 2.0 manufactured by Tana Netting FZE and produced at the contract manufacturing site HSNDS in Lahore, Pakistan. Though the information provided to PQI cannot directly attribute the concerns raised regarding DawaPlus 2.0 to the formulation/design of the product, there is uncertainty regarding the quality and efficacy of the product given the weight of evidence collected through the post-market complaint process.

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In January 2019, the ownership of the Tana Netting FZE product Dawaplus 2.0 was transferred to NRS Moon Netting FZ and renamed Tsara Soft. The Post PQ Change (PPQC) application included verification from NRS Moon Netting FZ that Tsara Soft was identical to Dawaplus 2.0 and therefore the decision to convert Dawaplus 2.0 from WHOPEs to PQ should be extended to Tsara Soft. The PPQC application also included statements from both NRS Moon Netting FZ and Tana Netting FZE that both companies would support any on-going or future complaint investigations related to Dawaplus 2.0.

No complaints have been received in relation to Tsara Soft; however, since the transfer of ownership, additional complaints have been received for Dawaplus 2.0 products still in the channels of trade: pre-shipment storage, in transit, post-shipment; pre-distribution storage. These complaints, though identified in relation to Dawaplus 2.0, are considered to be reflective of Tsara Soft and therefore relevant to maintaining the validity of the supporting prequalification decision for Tsara Soft. It is unknown if the product has yet to be manufactured/distributed under the name Tsara Soft.

On 2 December 2019 WHO received an additional complaint presenting post shipment out of specification findings (low AI content) for Dawaplus 2.0. The supporting information and communication indicated that manufacturing issues persisted outside of the previously declared timeframe.

This letter is therefore to formally inform you that the prequalification of Tsara Soft (PQ Ref # 028-003) also known as Dawaplus 2.0, has been suspended from 12 December 2019 due to the uncertainty of product quality and efficacy. Upon assessment of the complete dossier to support the product as current formulated/manufactured, this decision will be reviewed.

Yours sincerely,



Deus Mubangizi
Coordinator
WHO Prequalification Team