Prequalification of Vector Control Products: A Workshop on the Process

The Cast

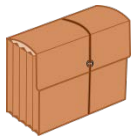
Dominic Schuler – PQT-VC Case Manager
Luis Perez Albela Vera – PQT-VC Product Chemist
Jess Rowland – ASVCP Expert: Toxicology and Risk Assessment
Charles Wondji – ASVCP Expert: Entomology
Special Appearance by Group Lead Marion Law

The Program

The Overture – An overview of the process

Stage 1: The Determination of Pathway

Intermission – Coffee Break



Stage 2: Pre-submission: Dossier Development

Stage 3: Submission: Filing an Application

Stage 4: Screening for Completeness

Intermission – Lunch

Stage 5a: Assessment

Intermission – Coffee Break

Stage 5b: Inspection

Stage 6: The Decision Making Process

Stage 7: Post-Prequalification Activities

The Overture

Why are we holding this Workshop?

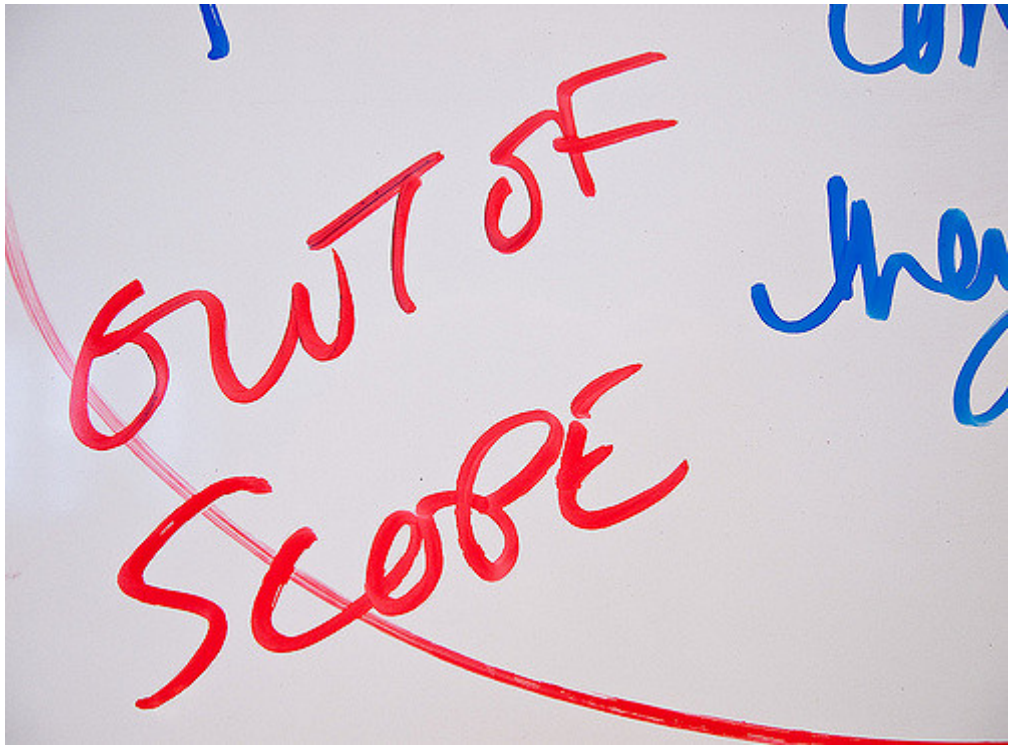
- This workshop is about the **process** which has been established for the prequalification of vector control products
- After a year of implementing this process we can now present on **facts** as compared to **theory**
- There is continued confusion and misinformation among stakeholders due to significant shifts in approach as compared to prior systems – we are here to solve that problem

Objectives

- Ensure attendees have a clear understanding of the **process** for the prequalification of vector control products

This workshop is *NOT* about…

- Specific product types nor a specific product
- Data requirements / study design / testing guidelines
- Comparative analysis of regulatory approaches



What are all those numbers?

Introduction to the Process of Prequalification

Are there fees associated with the prequalification of vector control products?

- Currently, there are **NO FEES** associated with the prequalification of vector control products nor the setting of specifications through JMPS

- Fee for service models are being investigated
- Implementation of fees will be conducted with stakeholder consultation

PQT-VC is the **single point of entry** for inquiries and submissions to WHO for the evaluation of vector control products

PQT-VC Utilizes a Service Based Approach

- PQT-VC offers particular services
- Applications are requests for a particular service
- An applicant submission is referred to in-house as an **action**
- The process and timeline for an action is dependent upon the service requested

Service Codes

Service Code	Service
PQ100	Request for Determination of Pathway
PQ200	Protocol Review
PQ300	New Vector Control Product
PQ301	New Equivalent Vector Control Product
PQ400	Active Ingredient: New Manufacturing Site
PQ401	New Active Ingredient Hazard Assessment via JMPR
PQ500	Post PQ Change: Major
PQ501	Post PQ Change: Minor

The Determination of Pathway

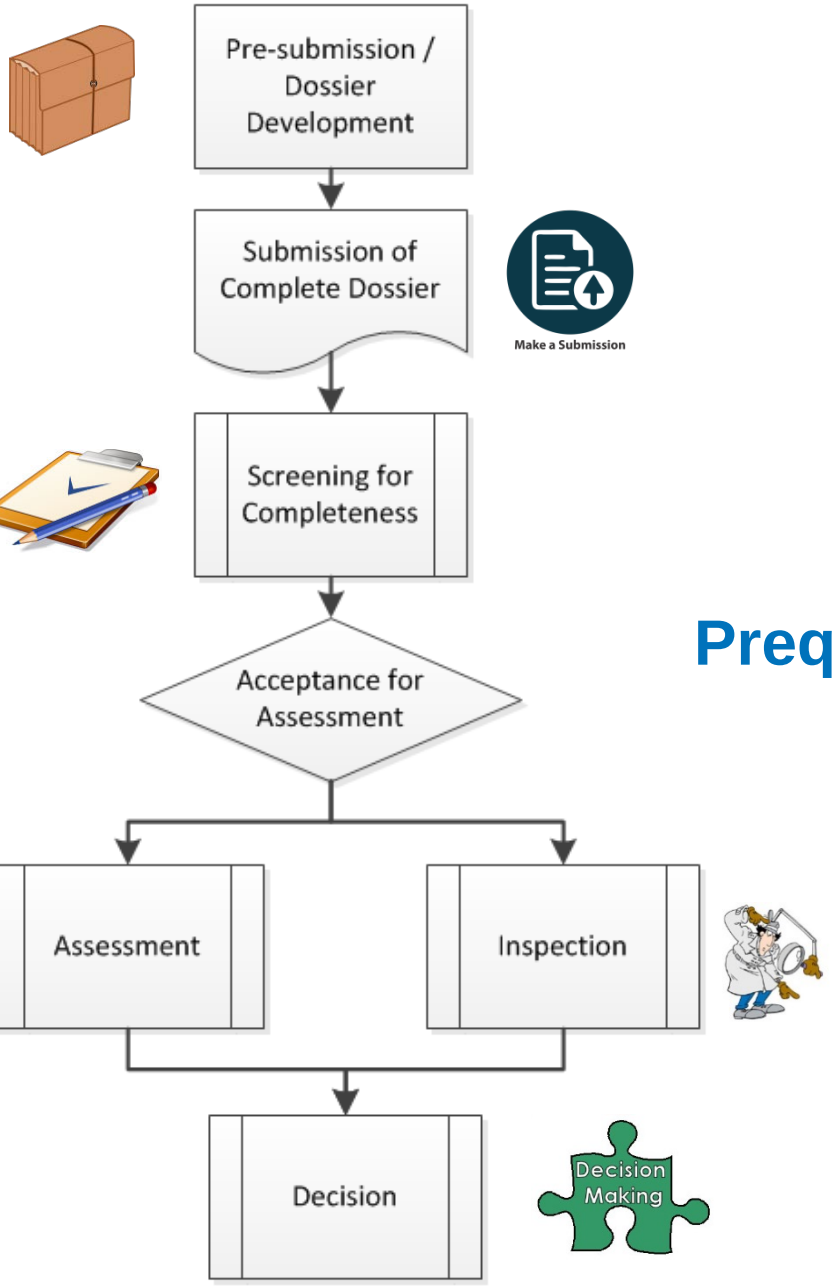
- The **first step** for every new product is The Determination of Pathway.
- This process enables WHO to provide manufacturers with the most applicable guidance regarding the data requirements and specific process to reach prequalification
- Outcomes:
  - Prequalification Pathway
  - New Intervention Pathway

Prequalification Pathway

- Assessment of:
  - Quality
  - Safety
  - Efficacy
- Inspection of manufacturing facilities

- …throughout the life of the product

Prequalification Pathway

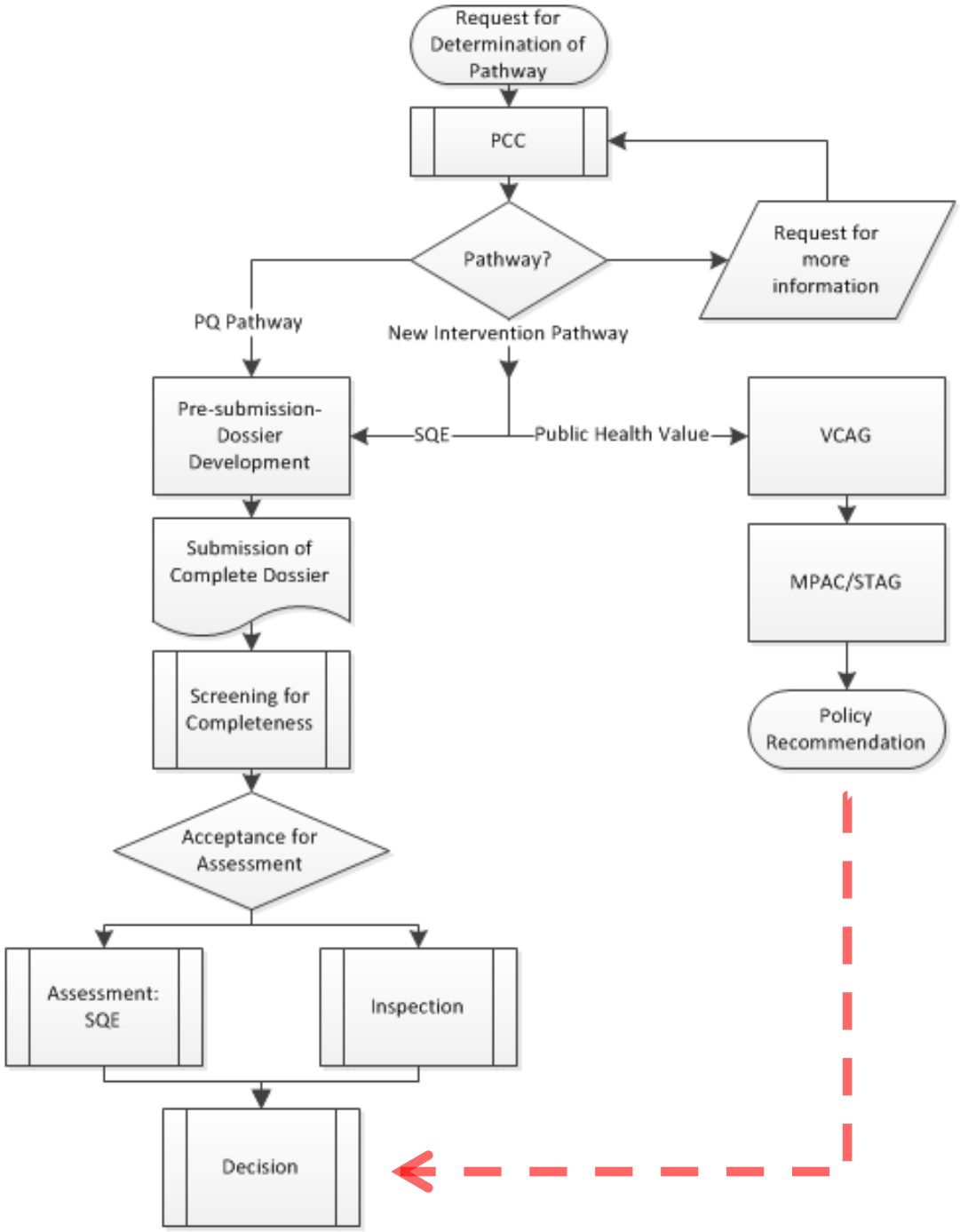


New Intervention Pathway

- Requires an assessment of *public health value*
  - Conducted in conjunction with WHO partners

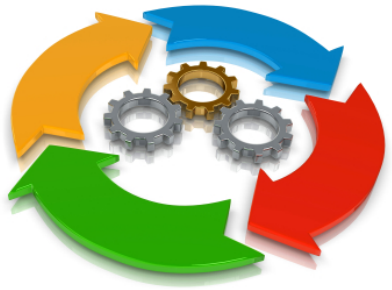
- The Prequalification Pathway still applies and is the same for the assessment of Quality, Safety and Efficacy

- Coordination and timing of assessments between the PQ process and assessment of public health value are case specific



New Intervention Pathway

Post-Prequalification Activities



- Addressing post-prequalification commitments
- Post PQ Changes
- Complaints
- Re-inspection

- Products may be suspended or delisted for failure to comply with stipulated requirements

End Scene – Preparations for Stage 1 in progress .....

Stage 1: The Determination of Pathway

The Determination of Pathway: Key Points

- WHO reviews applicant submitted Requests for Determination of Pathway (RDP) to determine if the proposed product/claim would be supported by existing WHO policy recommendations.

- The submission of an RDP is confidential and there is no obligation for the applicant to pursue the proposed product/claim.

- An RDP must be submitted for all new vector control products (VCPs), even those which claim equivalence to a reference prequalified product.

Requests for Determination of Pathway (RDP) Submission

- Cover letter requesting Service **PQ100**
- Request for Determination of Pathway Form
  - Handout
- Draft Label (if available)
- Additional supporting documentation

- Submit to the PQT-VC Case Managers via pqvectorcontrol@who.int

Pre-submission Coordination Committee (PCC)

- Coordinated by PQT-VC
- Includes representatives from the Global Malaria Program (GMP) and Department for Control of Neglected Tropical Diseases (NTD)

Pre-submission Coordination Committee (PCC)

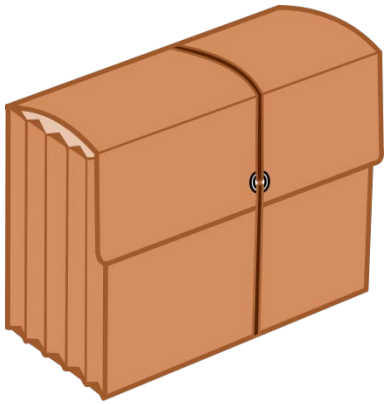
- RDPs are presented and the following items addressed:
  - Description of the proposed product/claim and its use pattern(s), the active ingredient(s), mode of action, and country registration status.
  - Which diseases is the product intended to impact through the expected effect (kill, repel, mitigate) on the target vector?
  - Is the proposed product/claim supported by an existing policy recommendation? If no, can an existing policy recommendation be expanded to support the product based on entomological efficacy data?

PCC Outcomes

- Prequalification Pathway
- New Intervention Pathway
- To Be Determined
  - The applicant will be contacted to provide the necessary clarification for a determination of pathway to be made

End Scene – Preparations for Stage 2 in progress .....

Stage 2: Presubmission/Dossier Development



http://www.who.int/pq-vector-control/resources/presubmission/en/

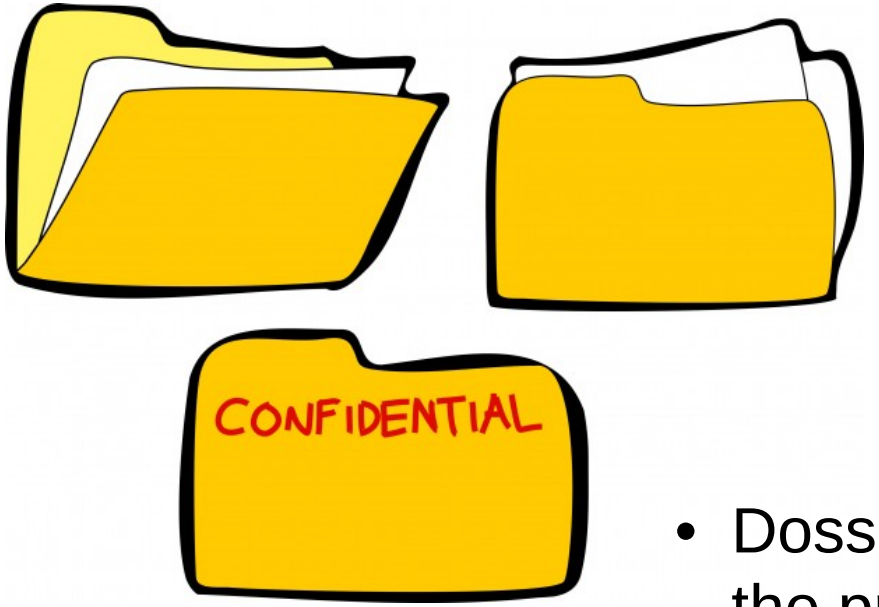
Where do I even begin?

Meeting Requests

- Meeting Request Form

- Submit to the PQT-VC Case Managers via pqvectorcontrol@who.int

The Dossier



- A dossier is compilation of letters, forms, studies (data), and other supporting documentation

- Dossiers are updated over time as the product changes or new information is submitted

Dossier Development

- The responsibility for the compilation of a complete product dossier is solely that of the applicant/manufacturer

- PQT-VC cannot assist in identification, selection of nor negotiation with contract research organizations (CRO)

GLP Requirement

- All supporting studies supporting a prequalification application must be generated in accordance with Good Laboratory Practices (GLP).
- If studies are submitted which were not conducted in accordance with GLP, then a rationale must be provided as part of the submission.

Dossier Format – The Module Approach

- This is not an additional requirement
- This is just a format

Dossier Format – The Module Approach

- Why?
  - Easier dossier compilation and editing
  - More efficient screening and reviews
  - Consistent structure to support collaborative work with countries

Dossier Format – The Module Approach

- Module 1: Administrative information and labelling
- Module 2: Discipline summaries
- Module 3: Quality dossier
- Module 4: Safety dossier
- Module 5: Efficacy dossier
- Module 6: Inspection dossier

Dossier Format – The Module Approach

- How did we get to this?
  - Experience from conversions and a review of Country level, OECD, and eCTD dossier structuring models
- Timing of implementation:
  - As new submissions are developed
- Would it be worth having a dossier workshop?

Module 1: Administrative information and labelling

- Cover letter
- Application form
- Table of Contents
- Letter(s) of authorization
- Letter(s) of access
- Declaration of Labelling

Cover Letter

VCP UNLIMITED
Example Company
Global Office in Malaysia

Dear PQT-VC

We are pleased to submit a new product application (Service Code PQ300) for the product **Pro Protect** for your review and consideration for prequalification.

We have compiled the dossier in the requested format:

- Module 1: Administrative information and labelling
- Module 2: Discipline summaries
- Module 3: Quality dossier
- Module 4: Safety dossier
- Module 5: Efficacy dossier
- Module 6: Inspection dossier

The Table of Contents has been included in Module 1 to support the efficient screening and review.

Sincerely yours,

J. Duckworth

Application Form and Table of Contents

- Handouts

Letter of Authorization

VCP UNLIMITED
Example Company
Global Office in Malaysia

Dear PQT-VC,

Please be informed that VCP Unlimited hereby authorizes **Beatrice Agent** of the company **Expert Regulatory Consultants** to represent VCP Unlimited in all matters related to the new product application for prequalification of the product Pro Protect.

Sincerely yours,

J. Duckworth

Letter of Access

GREAT BIG CHEMICALS
Example TGAI Company

To whom it may concern,

Great Big Chemicals, the producer of the active ingredient Chlorophosphoorganobetaehtrin, confirms that **VCP Unlimited** is a recipient of our Technical Grade AI for the purposes of production of the product Pro Protect. VCP Unlimited is authorized to submit the data specified in the attached appendix in support of this product from Great Big Chemicals.

Sincerely yours,

Annabel Owner

Labelling and PQT-VC

- PQT-VC does not register products and therefore does not approve labelling
- Label information is required to inform the evaluation of the product. Clarification on label content may be requested
- PQT-VC may provide comments on label language based on the evaluation of the supporting data

Declaration of Labelling

- Focus is on the label content

- Standard Format for submission to PQT-VC
  1. Product Identification
  2. Ingredient Statement
  3. Safety
  4. Directions for Use
  5. Product Claims

Use of WHO Name or Logo

- The WHO name and emblem, may not be used by manufacturers or any other party for commercial and/or promotional purposes

Module 2: Discipline summaries

- Data and manufacturer conclusions are summarized in three documents:
  - Summary of Quality Dossier
  - Summary of Safety Dossier
  - Summary of Efficacy Dossier

Module 3: Quality dossier

- Compilation of supporting information:
  - Physical/Chemical Data
  - Declaration of Product Formulation
  - Description of Manufacturing Process
  - Declaration of Manufacturing Sites
  - Confidential Appendices

Module 4: Safety dossier

- Compilation of supporting information:
  - Acute toxicology (6-pack)
    - Acute Inhalation
    - Acute Oral
    - Acute Dermal
    - Primary Eye Irritation
    - Primary Skin Irritation
    - Dermal Sensitization
  - Product Risk Assessment (Occupational and Residential Exposure)
  - AI Specific Hazard Assessment (or summary of publically available information)

Module 5: Efficacy dossier

- Compilation of supporting information:
  - Lab studies
  - Field studies

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Module 6: Inspection dossier

- Compilation of supporting information:
  - Site Master File(s)

Hey! How about some context, huh?

Service Codes

Service Code	Service
PQ200	Protocol Review
PQ300	New Vector Control Product
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PQ400	Active Ingredient: New Manufacturing Site
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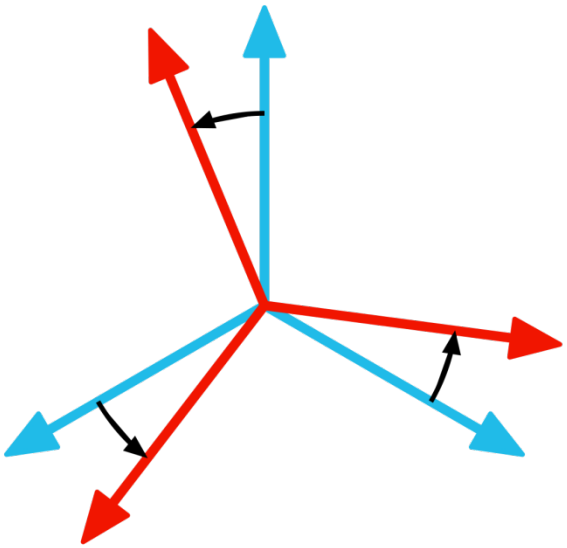
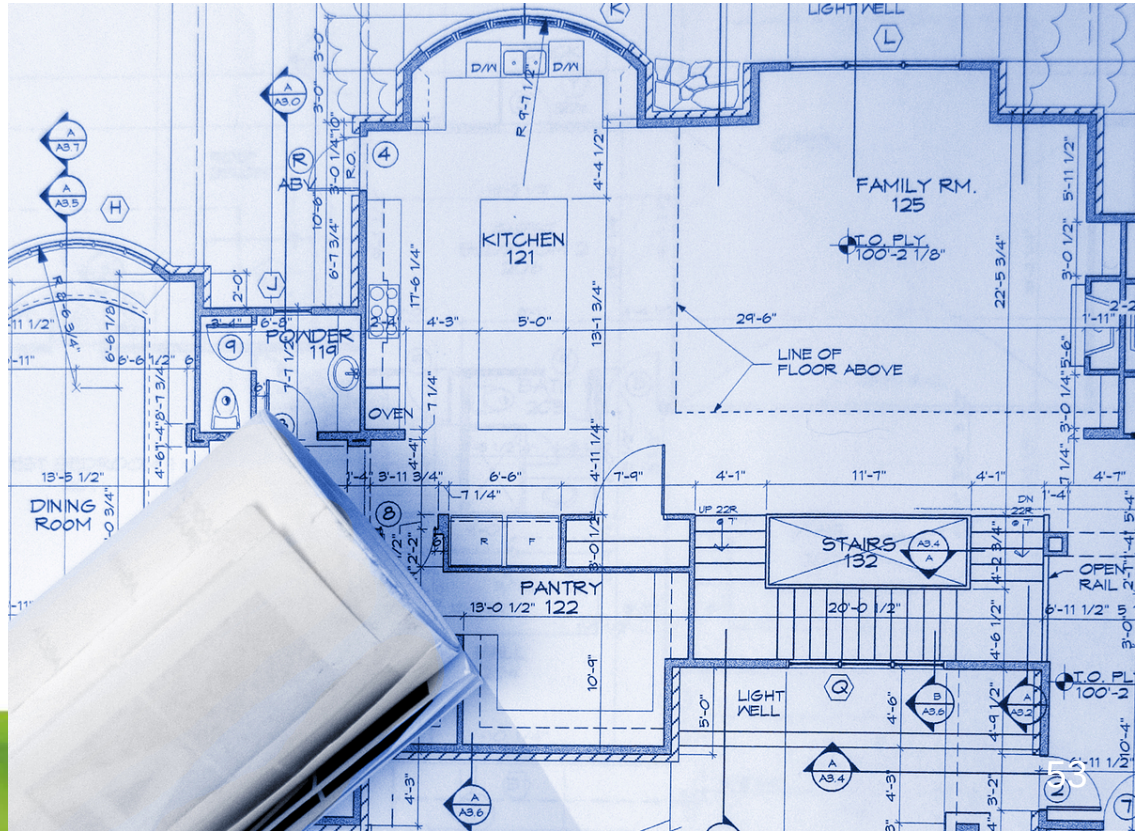
PQ500	Post PQ Change: Major
PQ501	Post PQ Change: Minor

Service Codes – Presubmission Actions

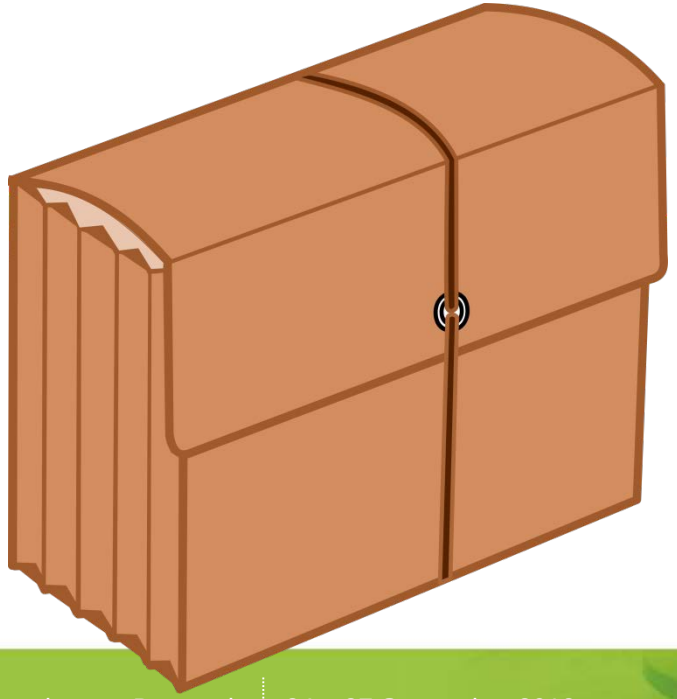
Service Code	Service
PQ200	Protocol Review





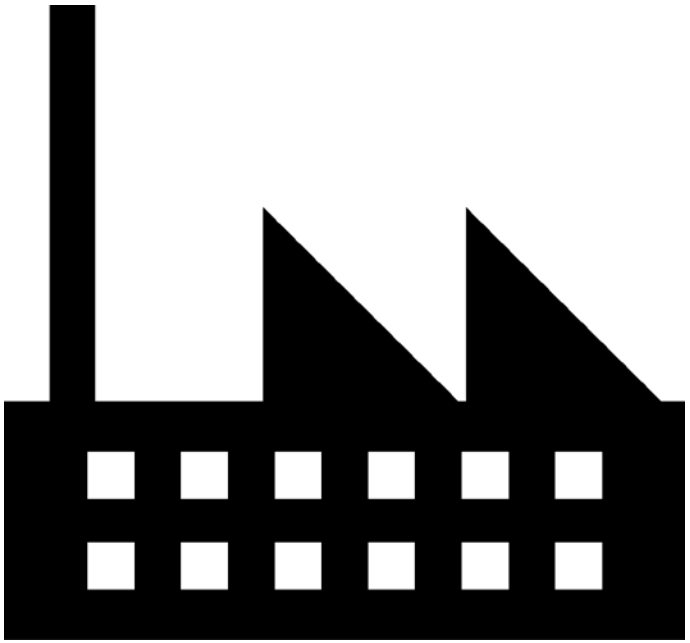
Service Codes – New End Use Products

Service Code	Service
PQ300	New Vector Control Product
PQ301	New Equivalent Vector Control Product



Service Codes – Active Ingredients

Service Code	Service
PQ400	Active Ingredient: New Manufacturing Site (TC/TK Specification)
PQ401	New Active Ingredient Hazard Assessment via JMPR



Service Codes – Changes to Prequalified Products

Service Code	Service
PQ500	Post PQ Change: Major
PQ501	Post PQ Change: Minor

End Scene – Preparations for Stage 3 in progress .....

Stage 3: Filing a Submission

Filing a submission

- All applications to PQT-VC should be submitted in **electronic form** and be supplemented by **one (1) hardcopy**.
- Individual documents do not need to be password protected if a secure transfer method is used.

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Methods of submission:

- MedNet - Submitting Information to PQT using MedNet.pdf
- Password protected CD or DVD sent via mail (Password should be sent separately or by email to pqvectorcontrol@who.int)
- Other secure web-based file transfer service
- Mail:

  WHO Prequalification Team
  Vector control products
  MVP/EMP/RHT/PQT
  World Health Organization
  20, Avenue Appia
  1211 Geneva 27
  Switzerland

What is MedNet?

- MedNet is a secure file transfer platform for WHO
- Upon request from a manufacturer, PQT-VC will create a company specific sub-community

- The manufacturer is responsible for identifying the authorized users by providing their names and email addresses
- The manufacturer is responsible for communicating to PQT-VC any changes to the authorized users

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Confirmation of Receipt

- Upon receipt of an application, PQT-VC will send an email to the primary point of contact identified on the application form to confirm receipt of the submission

PQT-VC: Logging in the submission

- Assign a PQ Ref #
  - Company Number-Product Number [ccc-ppp]
  - Ex. 005-001
- Assign an action ID
  - New Product – [NP20yy-xxx]
  - Post PQ Change – [PPQC20yy-xxx]
  - Presubmission Request – [PR20yy-xxx]

End Scene – Preparations for Stage 4 in progress .....

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Stage 4: Screening

Why conduct a screen?

- Administrative
  - Ensure that the submission is complete and there are no missing documents/modules
  - Review the Cover Letter/Table of Contents and cross reference against the submission

- Technical
  - Identify issues/gaps within the modules which need clarification in order to support the assessors' review

- Prepare now, ensure efficiency later

Screening Outcomes - Letters

- Request for Information (RFI)
  - If deficiencies are identified (Administrative or Technical) an RFI letter will be sent to the applicant.

- Acceptance for Assessment (AFA)
  - If the submission is deemed complete, an AFA letter will be sent to the applicant
  - An AFA letter may contain clarifying questions for which a requested submission date will be provided

- Screening Failure
  - Your journey is not over! You may resubmit your application at a time when identified deficiencies have been addressed

End Scene – Preparations for Stage 5 in progress .....

Stage 5a: Assessment

The Assessment Session for Vector Control Products (ASVCP)

- Frequency – 2 times per year (minimum)
- Held around the world
- Closed meetings
- Conducted in accordance with adopted SOPs:
  - SOP 1 – Process of the ASVCP
  - SOP 2 – Format of Data Reviews and PQ Listing Decision Document
  - SOP 3 – Dispute Resolution
  - SOP 4 – PQ Listing Decision Process and Documentation

ASVCP: During and Between Meetings

- Assessment of New Product Applications are initiated at the next ASVCP
- Reviews that are not completed at a session are continued between sessions
- Assessors are kept on contract between ASVCP meetings to support continued assessments and other PQT-VC initiatives

Preparation for an ASVCP Meeting

- Collation of all applications to be reviewed
- Assignment of assessors
- Ensuring access to dossiers
- Preparation of materials

Typical Agenda

Day	Agenda Items
Monday	Update on PQT-VC; Update on Pending Applications; Assignment of New Applications; Individual work
Tuesday	Individual work; Discipline Specific Meetings; Closing Group Discussion
Wednesday	Site Visits – Local Manufacturing/testing/research facilities; guest speakers; meetings with local regulators/stakeholders
Thursday	Individual work; Discipline Specific Meetings; Closing Group Discussion
Friday	Individual work; Recap of week; Confirmation of continuing assignments

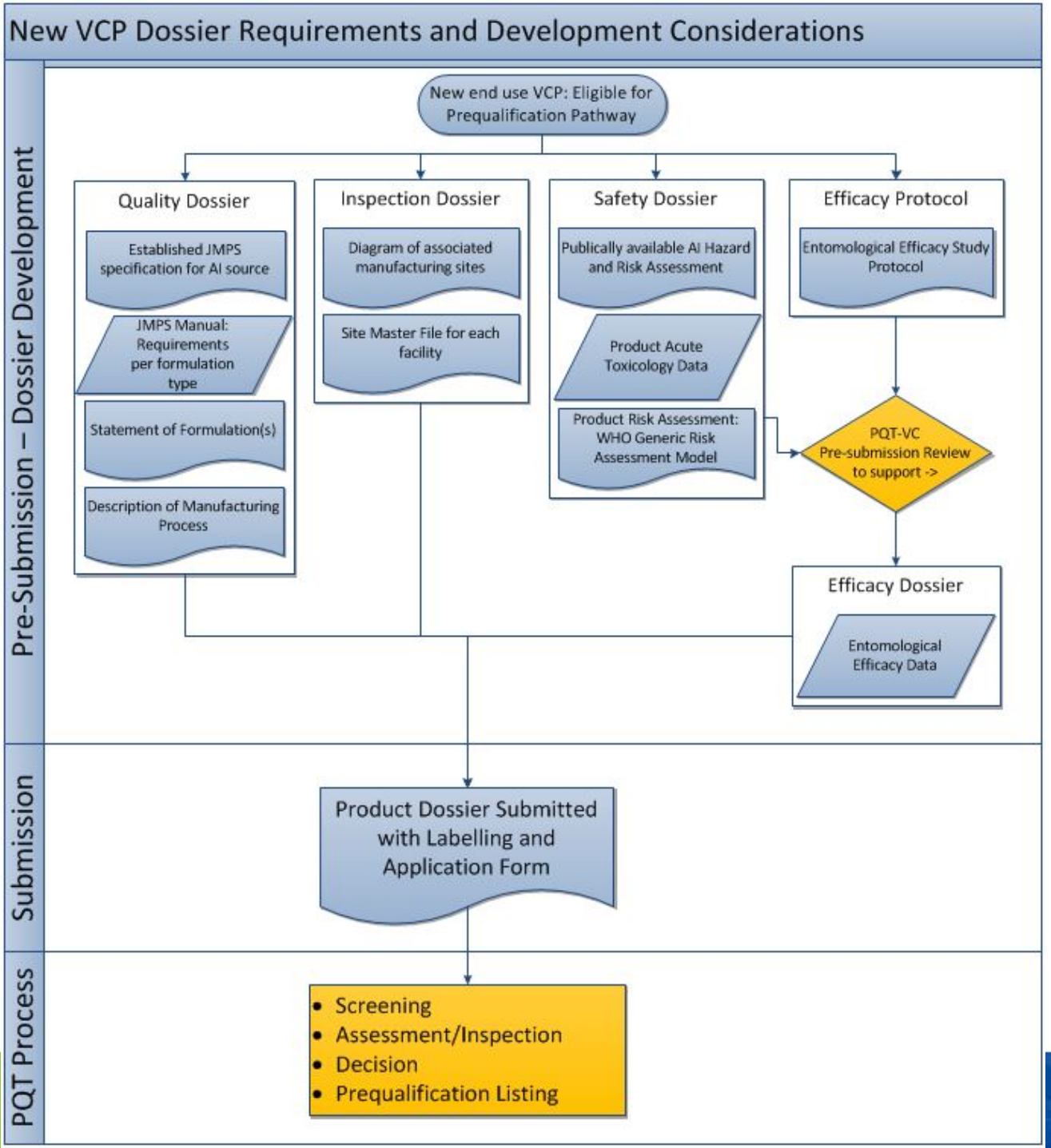
General Process

- Assessors familiarizes themselves with the assigned application in collaboration with PQT-VC Staff/Screening Officer
- Review individual studies and generate a Data Evaluation Record (DER)
  - Identify questions/deficiencies to be addressed by the applicant
  - Determine if the study is acceptable for use in decision making
- Peer Review Process
- Draft a Discipline Summary Document to convey conclusions across submitted studies

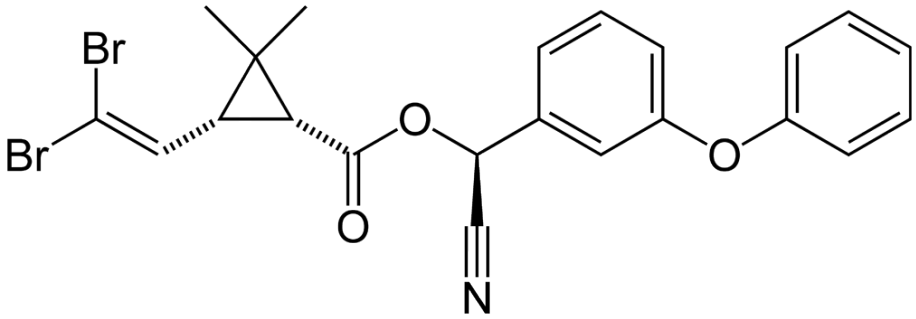
Requests for Information (RFI)

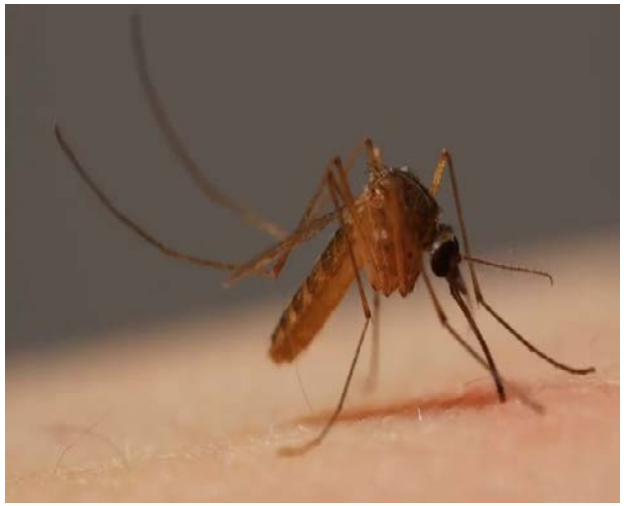
- Applicants will be informed of questions/deficiencies through an RFI letter
- Depending on the timing of parallel dossier component reviews, one or more RFIs may be sent
- Information provided by the applicant in response to an RFI will be reviewed as it becomes available
  - **<u>ASSESSMENT WILL CONTINUE BETWEEN MEETINGS</u>**

New VCP Dossier Requirements and Development Considerations



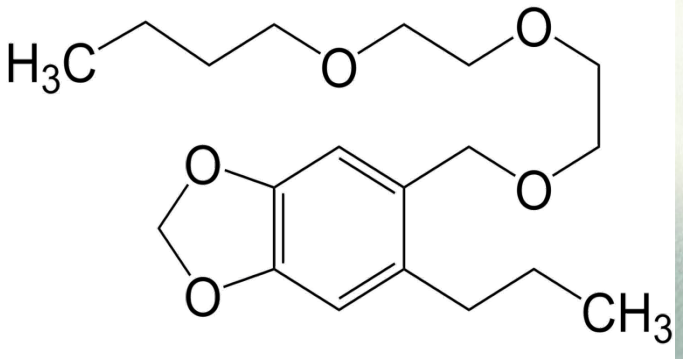
Chemistry and Specifications of Pesticides for Vector Control Products





- Dr. Luis Perez Albela
- Scientist Product Chemist
- Prequalification-Vector Control WHO

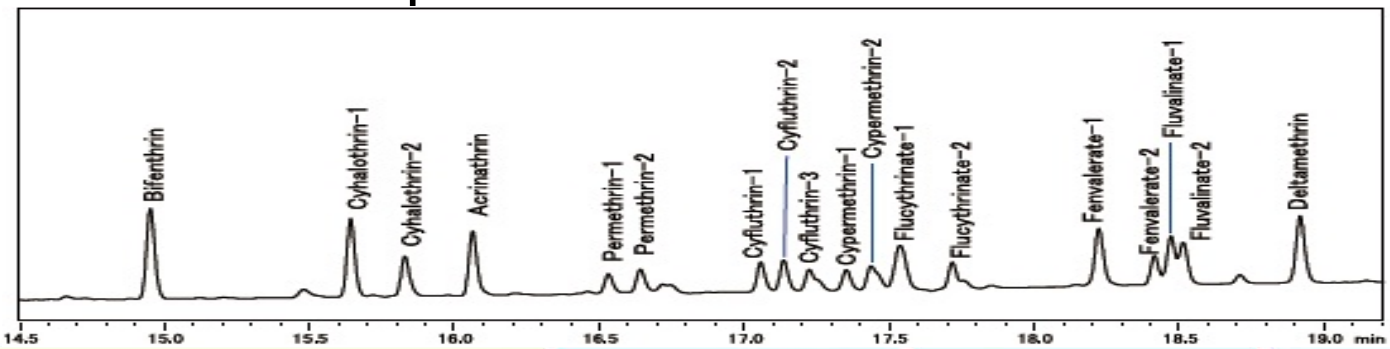
Outline of presentation



- Importance of pesticide quality standardization
- Specifications guidelines for WHO PQT-VC products
- Quality components for PQT-VC products
- Example of chemical specifications
- Data required in the Quality dossier
- Additional WHO technical information

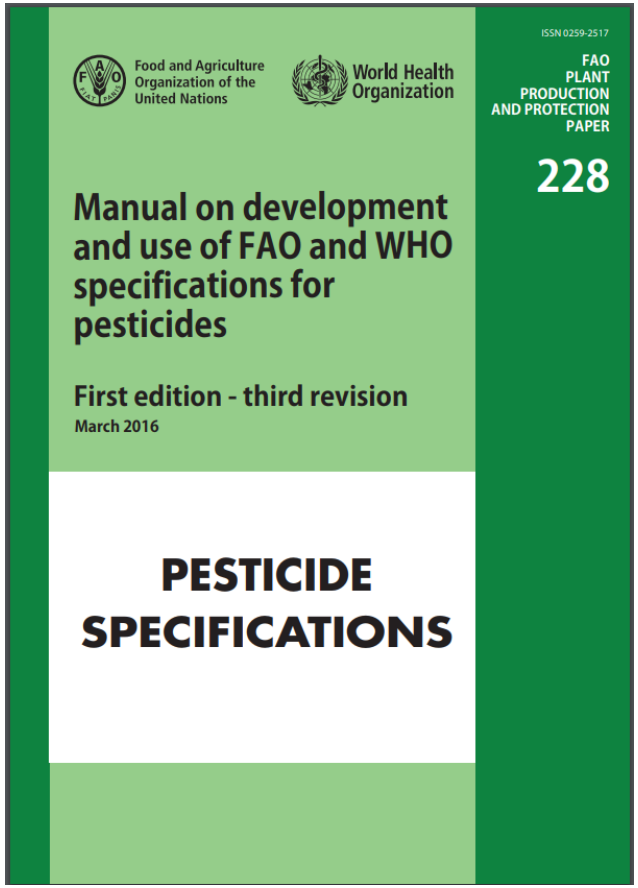
Importance of Pesticide specification in PQT-VC

- Basic criteria for quality acceptance
- Quality standardization of vector control products and technical concentrates
- Acceptability of analytical and physical test methods
- CIPAC methods
- Methods must be peer-validated, all supporting information must be provided



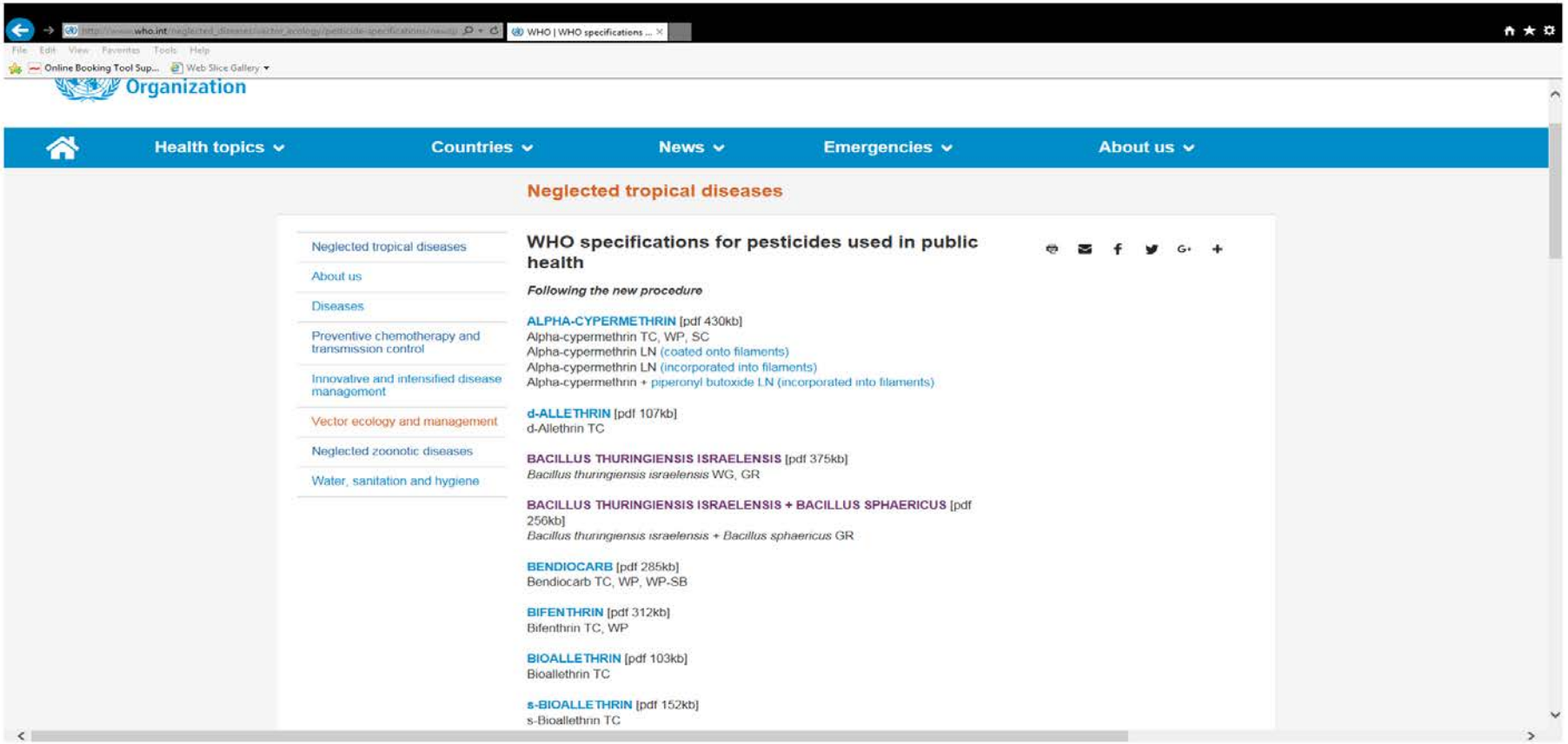
Guidelines and Product Information

- The ***FOUNDATION*** of pesticides specification for WHO-PQT-VC
- All relevant information for TC and product specification
- Chemical composition and product type
- Physical/Chemical Characteristics
- Storage Stability



http://www.who.int/whopes/resources/9789251092651/en/

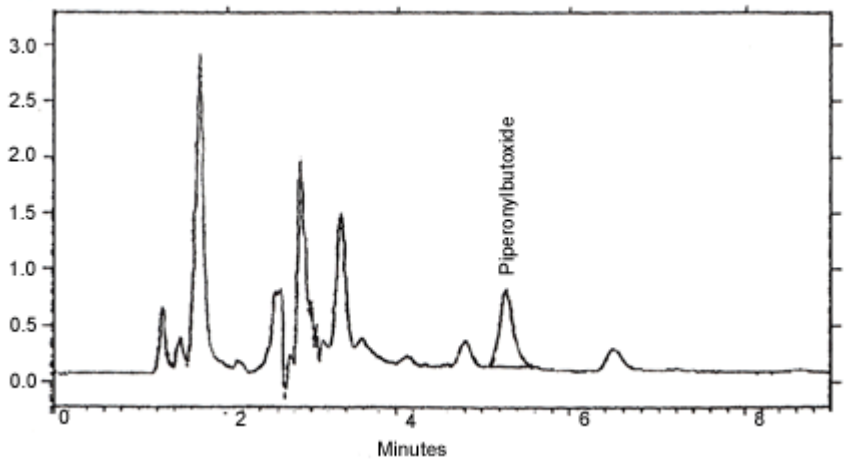
WHO Specifications for pesticides in public health



http://www.who.int/neglected_diseases/vector_ecology/pesticide-specifications/newspecif/en/

Quality specification criteria for vector control product

- Description of the product
- Active ingredient, content and formulation type
- Relevant impurities
- Physical properties
- Storage Stability
  - Residual content
  - Physical properties



Example of WHO Specification 8.21 long lasting insecticides nets

- Description of product
- Active ingredient
  - Active ingredient content
  - Wash resistance index
- Physical properties
  - Fabric weight
  - Netting mesh size
  - Dimensional stability after washing
  - Bursting Strengh
  - Flammability

- Storage Stability
  - Concentration of A.I.
  - Wash Resistance Index
  - Dimensional stability
  - Bursting Strength

Data requirement for active ingredient

A.1	**Identity of the active ingredient** (information only)	
	ISO English (E-ISO) common name and status	Y
	Any other common name or synonym.	Y
	Chemical name (IUPAC and CA).	Y
	CAS No. (for each isomer or the mixture of isomers, if appropriate).	Y
	CIPAC No.	Y
	Structural formula(e) (including stereochemistry of the active isomers).	Y
	Isomeric composition, if appropriate.	Y
	Molecular formula.	Y
	Relative molecular mass.	Y

Physical and chemical properties of active ingredient

Entry (studies and endpoint), pure active		
Melting point	Y	
Temperature of decomposition	Y	
Vapour pressure	Y	
Solubility in water	Y	
Octanol-water partition coefficient	Y	
Dissociation characteristics, if appropriate	Y	
Hydrolysis, photolysis and other degradation characteristics	Y	
Melting point of TC (active ingredients that are solids above 0 °C).	Y	
Studies and data for solubility in organic solvents at room temperature for pure or technical grade active ingredient.	Y	

Production process and impurities of active ingredient

A3	Outline of the route of manufacture	Y
A.4	Minimum active ingredient content.	Y
A.5	Manufacturing maximum limits for impurities present at or above 1 g/kg, supported by batch analysis data (minimum 5 typical batches)(all confidential data).	Y
A.6	Manufacturing maximum limits for impurities proposed as relevant at < 1 g/kg.	Y
A.7	Information on relevant impurities, with explanations of the effects observed (for example, toxicological effects, or effects on the stability of the active ingredient). Limits set by the FAO/WHO Joint Meeting on Pesticide Residues (JMPR) and/or registration authorities should accompany this information, identifying the authority responsible for setting the limit.	Y
A.8	Identity and nominal content (g/kg) of compounds intentionally added to the TC/TK (confidential data).	Y

Data require for active ingredient

A.9	Toxicological summaries (including test conditions and results)	Y
A.9.1	Toxicological profile of the TC/TK based on acute oral, dermal and inhalation toxicity; skin and eye irritation, skin sensitization.	Y
A.9.2	Toxicological profile of the TC/TK based on repeated administration (from sub-acute to chronic) and studies such as reproductive and developmental toxicity, genotoxicity, carcinogenicity, etc.	Y
	Equivalence: Data on in-vitro mutagenicity (*S. typhimurium*.) required in all cases including Tier-1 equivalence	
A.9.3	Ecotoxicological profile of the TC/TK based on toxicity to aquatic and terrestrial organisms (e.g. fish, Daphnia, algae, birds, bees), as appropriate to the intended use, and information of persistence.	Y
A.10.1	WHO classification by hazard.	Y
A.10.2	References to JMPR evaluations for toxicology, environmental fate and ecotoxicology should be given, where these exist.	Y

Data requirement for formulations

B.1	Identify if the formulations are for public health or agriculture uses, or both.
B.2	In the case of public health pesticides, confirm that the formulation and manufacturing process are the same as those employed for the materials evaluated by WHOPES for efficacy.
B.3	List the main formulation types available and identify those for which specifications are sought.
B.4	List the main countries where these formulations are registered and sold or, if there are very many, give the number of countries in each region or continent.
B.5	Physical properties, as required by sections 5 to 9 of this Manual. If necessary, briefly explain why it is proposed that certain clauses should be deleted, new clauses should be inserted, or less stringent limits should be adopted compared with those given in the guideline specifications.

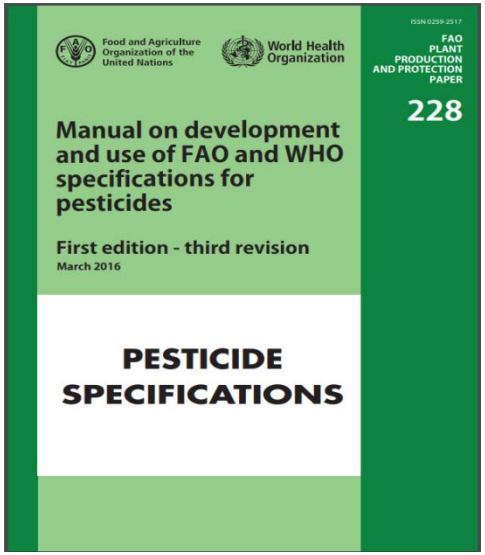
Formulation, Manufacturing Process, Description of Manufacturing site, Quality Accreditation

Methods of analysis of TC and formulations

C.1	At least two methods for testing identity of the active ingredient and one for testing the identity of the counter-ion or other derivative, if appropriate.	Y
C.2	Method for determination of active ingredient content. The method needs to be collaboratively validated.	Y
C.3	Methods of analysis for relevant impurities, in detail, including validation data, if not published. Give the principle of the methods of analysis used for non-relevant impurities in the TC/TK (GC with FID, for example).	Y
C.4	Reference test methods for physical-chemical properties.	Y
C.5	Information on validation completed, in progress or planned for methods listed under C.2 and C.3.	Y

Reminders and Key Considerations

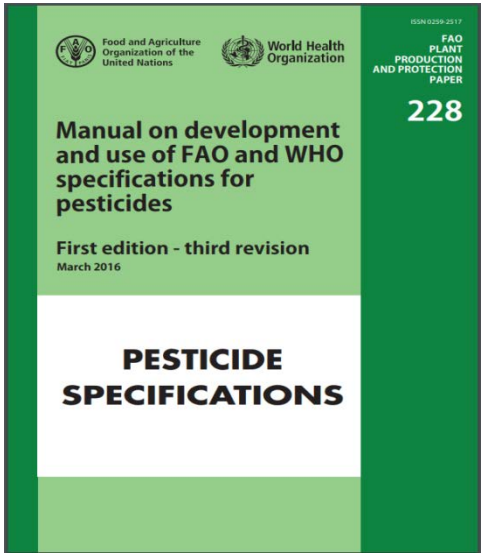
- More information is not always better
- Required basic information needs to be provided
- Follow the guidelines for TC and final product specification
- CIPAC methods https://www.cipac.org/
- If not CIPAC methods it must peer-review validated



http://www.who.int/whopes/resources/9789251092651/en/

Questions

?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Manual on development and use of FAO and WHO specifications for pesticides
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PESTICIDE SPECIFICATIONS

Hazard and Risk Assessment: Vector Control Products

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An Overview of Presentation

- ❑ Basic Concept of Toxicology
- ❑ Types of Toxicity Studies
- ❑ Toxicology Endpoint Selection Process
- ❑ Safety Assessment
- ❑ Acute 6-Pack
- ❑Data Evaluation Record (DER)
- ❑ Human Health Assessment
- ❑ Risk Assessment

Basic Concepts of Toxicology

- Toxicology studies are required to assess the hazard of a pesticide product.
- Animals are models to assess hazard and risk to humans from exposure to pesticide products due to shared biological characteristics.
- Toxicity studies are conducted in a variety of laboratory animals – mice, rats, rabbits, guinea pigs, dogs, monkeys etc.

Basic Concepts of Toxicology

- Multiple studies are needed determine cause-and-effect relationship (weight-of-evidence).
- Toxicity studies are designed to reflect (to the extent possible) “real life” exposure scenario.
- Adverse effects that are relevant to humans are selected for risk assessment.
- For each toxicity study, the lowest dose where adverse effects are seen (LOAEL) and the highest dose where NO adverse effects are seen (NOAEL).
- Assumptions: Humans may be up to 10X more sensitive than the most sensitive species tested.

Basic Concept of Toxicology

- 10 X Uncertainty Factor (UF) for using an animal study in human risk assessment (inter-species factor) (UF_A)
- 10 X UF because some people may be more sensitive than others (intra-species factor) (UF_H)
- 10 X UF for the use of a LOAEL (not a NOAEL) (UF_L)
- 10 X UF use of short term study for long term risk assessments (UF_s)
- 10 X UF for incomplete toxicity database (UF_{DB})
- 10X Safety Factor to account for sensitivity of pesticide exposure to children.

Acute Toxicity Studies: Product Specific

Initial step for hazard characterization, classification and labeling

- Acute oral toxicity -- Rat
- Acute dermal toxicity- - Rat or Rabbit
- Acute inhalation toxicity - - Rat
- Primary eye irritation--Rat
- Primary dermal irritation -- Rat
- Dermal sensitization– Guinea Pig

Subchronic Toxicity Studies – Active Ingredient

- 90-Day Oral (Gavage or Dietary) – Mouse, Rat
- 90-Day Oral (Gavage, Capsule or Diet) – Dog
- 90-Day Inhalation (Nose only or Whole body) – Rat
- 21/28-Day Dermal – Rat or Rabbit
- 90-Day Dermal – Rat or Rabbit

Chronic Toxicity and Carcinogenicity Studies: Active Ingredient

- Chronic Toxicity – Dog and Rat
- Carcinogenicity – Mouse and Rat

Developmental and Reproductive Toxicity Studies

- Prenatal Developmental Toxicity – Rat and Rabbit
- Multi-generation reproduction – Rat
- Developmental neurotoxicity – Rat

Mutagenicity Studies and Other Studies: Active Ingredient

- Bacterial reverse mutation assay
- *In vitro* mammalian cell assay
- *In vivo* cytogenetics

Other Studies

- Metabolism and Pharmacokinetics
- Companion animal safety
- Dermal penetration
- Immunotoxicity
- Acute Neurotoxicity

Use of Toxicology studies?

- Conclusions on the toxicity of a pesticide are based on a weight-of-evidence (WoE) approach
- Analyses and integration of the data of all studies
- Identify the sensitive endpoint/species
- Hazard Identification
- Dose-Response assessment
- Risk Characterization
- Risk Assessment

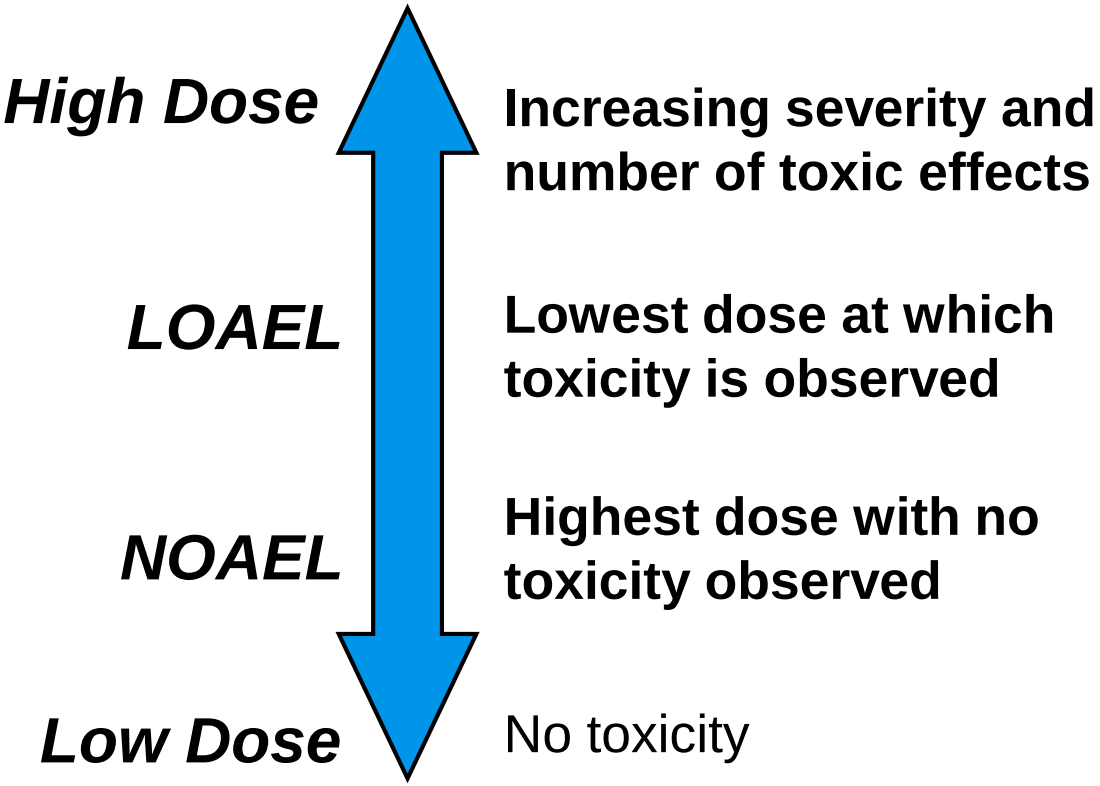
Toxicology Endpoint Selection Process: Endpoints for Exposure Scenarios

Hazard Identification & Endpoint Selection

- *Hazard*: Identification of harmful effects after oral, dermal and/or inhalation exposure to pesticide.
- *Dose:* Amount of pesticide (mg/kg/body weight/day)
- *Endpoint:* Harmful effect(s) of concern

- No observable Adverse effect level (NOAEL)
- Lowest observable Adverse effect level (LOAEL)
- Bench Mark Dose (BMD)
- Points of Departure (PoD) – NOAEL, LOAEL, or BMD

NOAEL and LOAEL & Dose Spread



Exposure Pathways & Routes of Exposure: Vector Control Products

- **Routes of Exposure:**

  Incidental Oral

  Dermal

  Inhalation

- **Exposure Duration:**

  Short Term (1–30 Days)
  Intermediate Term (1-6 Months)

  Long Term (>6 Months)

Reference Values

Acute Reference Dose (aRfD): A level at which a human can be exposed in one day without any adverse effects

Acceptable Daily Intake (ADI): European Agencies

Chronic Reference Dose (cRfD): A level at which a human can be exposed every day of a lifetime (chronic) without experiencing adverse effects.

$$\text{RfD/ADI} = \frac{\text{Point of Departure (e.g, NOAEL, LOAEL,BMD)}}{\text{Uncertainty Factor}}$$

Non-Dietary Exposure Scenarios

- **Incidental Oral** – Residential
- Evaluate hazard from hand to mouth behavior

Dermal – Occupational / Residential

- Evaluate hazard from dermal exposures

Inhalation – Occupational / Residential

- Evaluate hazard from inhalation exposure

Safety Assessment

- ✓ Safety Assessment: supporting data are assessed to ensure the safety of the product when used according to label directions.
- ✓ Includes sufficient detail to be a stand- alone document.
- ✓ Ensure all scientific principles, applicable guidelines and standards are adhered to
- ✓ Conduct according with the PQT-VC's Standard Operating Procedures (SOPs) to ensure uniformity in evaluation and timeliness of assessment activities.
- ✓ Incorporate into appropriate assessment documents (i.e., Data Evaluation Records (DERs) and Disciplinary Summaries, and Risk Assessments.

Safety Assessment

- Ensure appropriate level of details are included in the DERs and disciplinary summaries.
- Assure that study findings and conclusions are clear, concise and unambiguous.
- For each study, make a determination on the results of the study and whether the study is acceptable meeting guideline requirements.
- Disciplinary summaries should consist of a brief summary of each study used in the risk assessment.
- Conduct an in-depth review of publicly available hazard/risk assessments of the active ingredient.

Acute Toxicity Studies

- Purpose of these studies:

- Determine the toxic characteristics of a chemical.
- Provide data on health hazards from short exposures.
- Serve as a basis for toxicity classification and precautionary labelling.
- Use to calculate reentry intervals (e.g., after application of IRS products)..
- Develop personal protective-equipment (PPEs)(e.g. for operators).
- Inform on possible hazards from exposure of the eyes, mucous membranes and skin (skin and eye irritation studies).
- Provide data on skin sensitization.

Global Harmonization System (GHS) Categories

- Acute Oral, Dermal and Inhalation Toxicity

Acute toxicity	Cat. 1	Cat. 2	Cat. 3	Cat. 4	Category 5
Oral (mg/kg)	≤ 5	> 5 ≤ 50	> 50 ≤ 300	> 300 ≤ 2000	Criteria: • Anticipated oral LD50 between 2000 and 5000 mg/kg; • Indication of significant effect in humans;* • Any mortality at class 4;* • Significant clinical signs at class 4;* • Indications from other studies.* *If assignment to a more hazardous class is not warranted.
Dermal (mg/kg)	≤ 50	> 50 ≤ 200	> 200 ≤ 1000	> 1000 ≤ 2000	
Gases (ppm)	≤ 100	> 100 ≤ 500	> 500 ≤ 2500	> 2500 ≤ 5000	
Vapors (mg/l)	≤ 0.5	> 0.5 ≤ 2.0	> 2.0 ≤ 10	> 10 ≤ 20	
Dust & mists (mg/l)	≤ 0.05	> 0.05 ≤ 0.5	> 0.5 ≤ 1.0	> 1.0 ≤ 5	

Skin Corrosion / Irritation

Skin Corrosion Category 1			Skin Irritation Category 2	Mild Skin Irritation Category 3
Destruction of dermal tissue: visible necrosis in at least one animal			Reversible adverse effects in dermal tissue Draize score: ≥ 2.3 < 4.0 or persistent inflammation	Reversible adverse effects in dermal tissue Draize score: ≥ 1.5 < 2.3
Subcategory 1A Exposure < 3 min. Observation < 1 hr,	Subcategory 1B Exposure < 1 hr. Observation < 14 days	Subcategory 1C Exposure < 4 hrs. Observation < 14 days		

Eye Irritation

Category 1 Serious eye damage	Category 2 Eye Irritation	
Irreversible damage 21 days after exposure Draize score: Corneal opacity ≥ 3 Iritis > 1.5	Reversible adverse effects on cornea, iris, conjunctiva Draize score: Corneal opacity ≥ 1 Iritis ≥ 1 Redness ≥ 2 Chemosis ≥ 2	
	Irritant Subcategory 2A Reversible in 21 days	**Mild Irritant** Subcategory 2B Reversible in 7 days

Documentation: Data Evaluation Records (DERs)

Data Evaluation Record for Acute Oral Toxicity Study

Reviewer: **Date:**

STUDY TYPE: **Acute Oral Toxicity** – OECD No. 425 or EPA 870.1100

NAME OF PRODUCT TESTED:

TEST MATERIAL (% a.i.): (CAS#), Lot/ Batch #

STUDY TITLE:

STUDY NUMBER:

DATE OF STUDY:

TESTING FACILITY:

SPONSOR:

DER (Continued)

EXECUTIVE SUMMARY:

In an acute oral toxicity study, groups (#/sex) of strain, species (source, (age, weight) were given a single oral dose of (formulation, note a.i and purity %) mixed in (name of vehicle or undiluted test article) at doses of (XX) ppm or (XX)mg/kg bw. Animals were then observed for (#) days and sacrificed.

Oral LD_{50} Males = ____ mg/kg bw

Oral LD_{50} Females = ____ mg/kg bw

Oral LD_{50}Combined = _____ mg/kg bw

Using the GHS classification and labelling, this product is classified as Category ……

COMPLIANCE:

Signed and dated GLP statement: Yes/No
Signed and dated Quality Assurance statement: Yes/No
Signed and dated No Claim of Data Confidentiality statement: Yes/No

DER (Continued)

RESULTS and DISCUSSION:

A. Observations: (Survival, Clinical Signs, Body Weight , Gross necropsy, etc.)

B. Statistics: The oral LD_{50} was calculated using (indicate method used)

C. Deficiencies:

REVIEWER'S CONCLUSION AND RECOMMENDATION:

- Describe the effects on mortality, clinical signs, body, weight, food consumption, gross and histologic (if done) pathology. Determine the LD50 values for both sexes.
- State if the study is acceptable and satisfies the Guideline requirement

Primary Reviewer Signature: _____ Date: _____

Secondary Reviewer Signature: _____ Date: _____

Human Health Assessment of Active Ingredients

- Publicly available evaluations of registered AI's can be used as the starting point for risk assessments.

Agency	Available at:
Environmental Health Criteria Monographs	http://www.who.int/ipcs/publications/ehc/en/
European Food Safety Authority (EFSA) – Pesticide Risk Assessments	http://www.efsa.europa.eu/en/pesticides/pesticidesscdocs.htm
International Programme on Chemical Safety (IPCS)	http://www.who.int/ipcs/publications/cicad/en/
International Agency for Research on Cancer (IARC) Monographs on the Evaluation of Carcinogenic Risks to Humans	http://monographs.iarc.fr/ENG/Monographs/PDFs/index.php
Joint Meeting on Pesticide Residues (JMPR) Monographs and Evaluations	http://www.inchem.org/pages/jmpr.html
United States Environmental Protection Agency (USEPA) – Pesticide evaluations	https://iaspub.epa.gov/apex/pesticides/f?p=chemical

Human Health Assessment

- Hazard characterization: includes all relevant toxicology studies with the experimental design, nature of effects seen, their severity and sites, and the NOAELs and LOAELs.
- Acute Toxicity data on the technical product (active ingredient) and end-use product are critical for PQT-VC evaluations.
- Discussion of the dose-response assessment for health-based guidance values.
- Hazard Identification; Provide the rationale for the PoDs, endpoints of concern and UFs used in the risk assessment.
- Clearly identify the Acute Reference Dose (ARfD) and Chronic RfD; Acceptable Daily Intake (ADI)
- Identify the appropriate Tolerable Systemic Doses (TDS) which includes the ADIs set by JMPR or national regulatory authorities.
- Provide a Toxicity Profile of the Active Ingredient.

Risk Assessment: Hazard & Exposure Inputs

Hazard:

- **Acute Reference Dose (aRfD):** A level at which a human can be exposed in one day without any adverse effects (used for acute scenarios).

- **Acceptable Daily Intake (ADI) / Chronic RfD:** A level at which a human can be exposed every day of a lifetime (chronic) without experiencing adverse effects.

$$\text{RfD/ADI} = \frac{\text{Point of Departure (e.g, NOAEL, LOAEL,BMD)}}{\text{Uncertainty Factor}}$$

Exposure:

- Data on the proposed product use pattern/directions for use to estimate mixing, loading, application, and post application exposure.
- Use of the default values from the GRAM or chemical-specific data (e.g., inhalation residues, dermal absorption, salivary extraction factor) from laboratory studies.

Components of a Risk Assessment

- **Hazard Assessment:** Identification of observed effects, the dose/exposure levels at which those effects occurred, and the dose/exposure levels below which no adverse effects were seen.
- **Exposure Assessment:** Concerns insecticide/pesticide operators(applicators), mixers, loaders, residents of treated dwellings, bystanders and domestic animals.
- **Risk Characterization:** Involves comparing exposure estimates with tolerable systemic dose established during hazard assessment.

Risk Characterization

$$\text{Tolerable Systemic Dose (TSD)} = \frac{\text{Point of Departure}}{\text{Uncertainty Factors}}$$

$$\%\ \text{TSD} = \frac{\text{Total Systemic Dose}}{\text{TSD (Acute/Chronic)}} \times 100$$

$$\text{Ratio} = \frac{\text{Total Systemic Dose}}{\text{TSD (Acute/Chronic)}}$$

Ratio <1 is Acceptable risk

Ratio > 1 is unacceptable risk

PQT-VC Risk Assessment

- Assessors review manufacturer generated risk assessment to verify selected GRAM default parameters and review rationale for deviation from default.
- Risk assessments may include worst-case scenarios as well as scenarios assuming use of certain PPE
- Assessments will provide the acute toxicity profile of the product and a comprehensive toxicological profile of the active ingredient(s).
- Provide adequate rationale on the reference values (PoDs, endpoints, UFs, RfDs, ADIs) used in risk assessments.
- Characterize the human health risks by providing the % TSD and the risk ratio as recommended by GRAMs.
- Identify data deficiencies and recommendations for applicants to address the issue.

Thank You & Questions

Efficacy: Vector Control Products

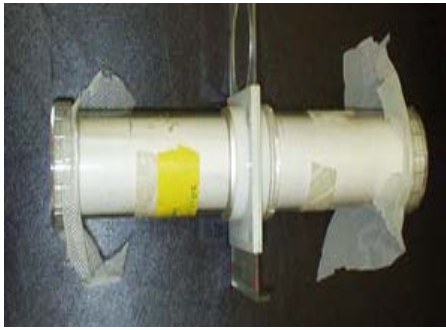
Charles Wondji
Entomologist
PQT-VC Team
World Health Organization

Supporting Information

- Lab and field testing required to establish efficacy of insecticide-based tools
- Various Phases provide different information on the efficacy of insecticides
- Phase I- Laboratory testing of the product
  - Intrinsic insecticidal activity of the product
- Phase II Field testing
  - Efficacy in semi-field conditions
- Phase III Large scale field trials
  - Demonstrate efficacy in real conditions (3 years) (e.g. durability, bio-efficacy, acceptance etc

Supporting information
Indoor Residual Spraying

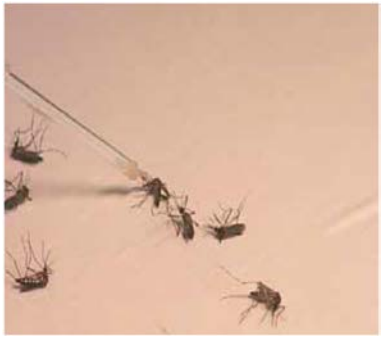
Phase	Type of study	Aim
Phase I	Laboratory studies	• Intrinsic insecticidal activity • Diagnostic concentration • Irritant or excito-repellent properties • Cross-resistance to other insecticides • Efficacy and residual activity on relevant substrates
Phase II	Small-scale field trials	• Efficacy and persistence under different ecological settings • Dosage of application • Handling and application • Perceived side-effects
Phase III	Large-scale field trials	• Efficacy and residual activity • Operational and community acceptance

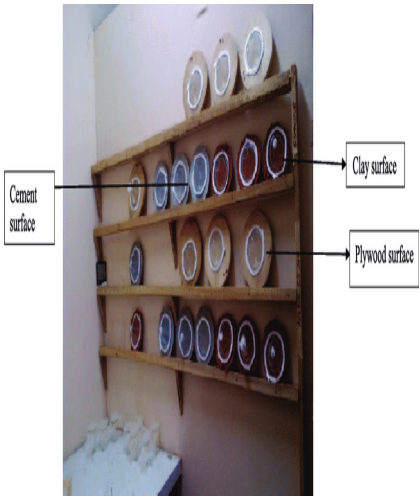


WHO, 2006

IRS Phase I laboratory testing

Purpose	Parameters measured	Listing thresholds
A. LABORATORY STUDIES (PHASE I)		
i) Intrinsic biological activity: To establish dose-response line(s) and determine the LD50 and LD90	24h mortality	No
ii) Excito-repellent / Irritant properties : To determine the irritant or excito-repellent properties	Cone bioassays Time to first take off	No
iii)Determination of optimal dose / efficacy and persistence on different surfaces: To test the residual activity of the insecticide formulation	-Knock down -Mortality after 24h	≥80% mortality or ≥95% KD
iv)Cross-resistance: To determine cross resistance: with other commonly used insecticides	24h mortality	No





IRS Phase II and III

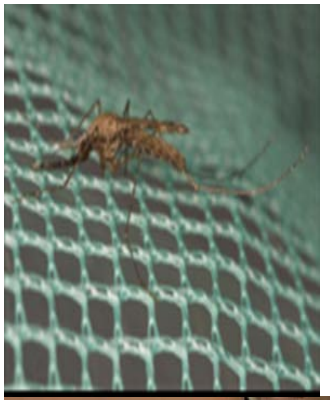
Purpose	Parameters measured	Listing thresholds
B. EXPERIMENTAL HUT TRIALS (PHASE II)		
To determine efficacy against a wild flying mosquito population, in settings relevant to the product claim	24h mortality, blood feeding inhibition Deterrence and exophily	Number of weeks over which the ≥80% mortality or ≥95% KD threshold is achieved
C. Operational trial (PHASE III)		
Determination the entomological impact and residual efficacy of IRS under field conditions Cluster randomized trial Questionnaire	- Human biting rate - Sporozoite rates - Vector longevity - Resting densities indoor and outdoor	number of weeks over which the ≥80% mortality or ≥95% KD

Supporting Information
Long Lasting Insecticidal Nets (LLINs)

Phase	Type of study	Parameters measured
I	Laboratory	Regeneration of insecticidal activity
		Efficacy and wash-resistance
II	Small-scale field trial	Wash-resistance
		Efficacy as measured by vector mortality and blood-feeding inhibition
III	Large-scale field trial	Long-lasting insecticidal efficacy
		Rate of loss or attrition of nets
		Physical durability of netting material
		Community acceptance
		Safety

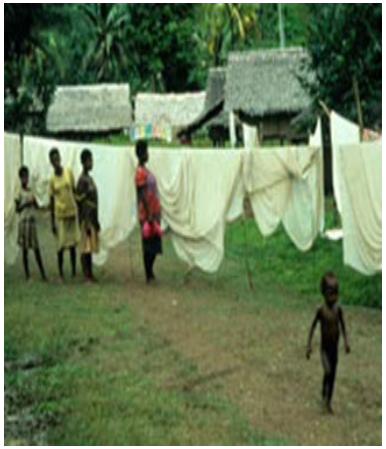
LLINs Phase I Laboratory testing

Purpose	Parameters measured	Listing thresholds
A. LABORATORY STUDIES		
i) Intrinsic biological activity: To establish dose-response line(s) and determine the LD50 and LD90	Topical application 24h mortality	No
ii) Excito-repellent / Irritant properties: To determine the irritant or excito-repellent properties	Cone bioassays Time to first take off	No
iii) Diagnostic concentration: To establish a diagnostic concentration for monitoring resistance to the insecticide in the field	Tarsal exposure in WHO tubes or modified CDC bottle assays -24h mortality	No
iv) Cross resistance: To determine cross resistance with other commonly used insecticides	Topical/contact 24h mortality	No
v) Regeneration time: To understand length of interruption of protection after washing. To inform washing procedures for later tests. Determining equivalency.	**cone bioassays/Tunnel tests** -60min knockdown -24h mortality -Proportion blood-fed	80% 24h mortality or 95% KD within 7 days following the wash.
vi) AI chemical content at baseline: To estimate within net and between net variation and the density of netting at baseline	Grams of AI per kg Mg of AI per square meter of netting	No
vii) Wash resistance: To determine whether minimum efficacy is achieved and maintained over a period of at least 20 laboratory and/or experimental hut type washes.	Cone: - Knock down after 60 minutes - Mortality after 24h Tunnel: - Blood feeding inhibition - Mortality after 24h	≥80% mortality or ≥95% KD in cone bioassays on nets washed 20 times or ≥90% KD blood-feeding inhibition in tunnel tests



LLINs Phase II and III

Purpose	Parameters measured	Listing thresholds
B B. EXPERIMENTAL HUT TRIALS		
Determine efficacy of LNs against a wild flying mosquito population, in settings relevant to the product claim	Deterrence, repellence, knockdown, mortality, blood feeding inhibition. Main parameters of interest depend on product claim and AI	A net washed 20 times should perform equal to or better than a positive control (LLINs already recommended
C. OPERATIONAL USE		
Determine the longevity of LNs under operational use as demonstrated either through longitudinal field trials OR Post-marketing operational sampling	Persistence of insecticidal efficacy: 24h mortality, KD and (in tunnel tests) blood feeding inhibition Retention of chemical content Physical integrity of netting material Reported adverse event	≥80% mortality or ≥95% KD in cone bioassays on nets after 3y field use or ≥90% KD blood-feeding inhibition in tunnel tests of nets after 3y field use



Larvicides testing

Phase	Type of study	Aim
Phase I	Laboratory studies	• Biopotency and activity • Diagnostic concentration and assessment of cross-resistance
Phase II	Small-scale field trials	• Efficacy under different ecological settings • Method and rate of application • Initial and residual activity • Effect on non-target organisms
Phase III	Large-scale field trials	• Efficacy and residual activity • Operational and community acceptance • Effect on non-target organisms

Larviciding Phase I Test

Purpose	Parameters measured	Listing thresholds
A. LABORATORY STUDIES		
i) Biological activity: To determine : -LC50 and LC90 or inhibition of adult emergency (IE50 and IE90). -Diagnostic or discriminating concentration.	48h larval mortality -Percentage of larvae that do not develop into successfully emerging adults, or adult emergency inhibition (IE%).	No
ii) Cross resistance: To assess cross resistance with other commonly used insecticides.	48h larval mortality or adult emergency inhibition (IE%).	No

Larviciding Phase II and III

Purpose	Parameters measured	Listing thresholds
B. SMALL-SCALE FIELD TRIALS		
i) Trials in natural breeding sites: - Efficacy under different ecological settings and residual activity	Efficacy and residual activity at different doses determined from post-treatment counts in treated and control sites compared to pre-treatment counts or control.	80% or 90% (the desired level of control) for a given dosage.
ii) Simulated field trials (if trials in natural breeding sites are not feasible):	Post-treatment mortality. Or inhibition of emergence of adults and the percentage reduction in larval and pupal densities.	80% or 90% (the desired level of control) for a given dosage.
C. LARGE SCALE FIELD TRIALS		
-Confirm efficacy, residual activity and application intervals -Record observations on ease of application and dispersal of the insecticide -Observe community acceptance -Record any perceived side-effects on operations -Observe the effect of the treatment of non-target organisms	Larval and pupal abundance – sampled pre and post treatment and compared	80% or 90% (the desired level of control) for a given dosage.

Space spray Phase I

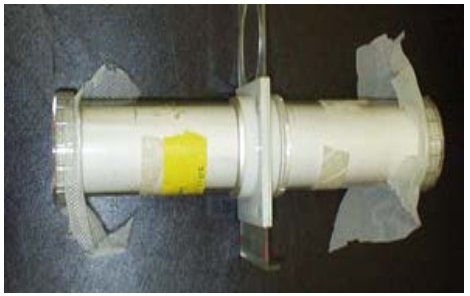
Purpose	Parameters measured	Listing thresholds
A. LABORATORY STUDIES		
i) Intrinsic biological activity: To establish dose-response line(s) and determine the LD50 and LD90	Topical application of an active ingredient. 24h mortality	No
ii) Intrinsic biological activity as a spray: To determine the LC50 and LC90 as determined by contact with insecticide spray.	Wind tunnel exposure to technical insecticide in acetone, in a range of doses. 24h mortality	No
iii) Diagnostic concentration for monitoring resistance: To establish a diagnostic concentration for monitoring resistance	Tarsal exposure of mosquitoes for 1h to insecticide deposits on filter paper 24h mortality	No
iv) Cross-resistance: To determine cross resistance with other commonly used insecticides	Topical/contact 24h mortality	No

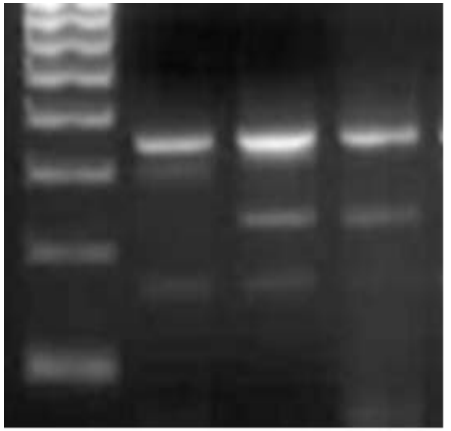
Space spray Phase II and III

Purpose	Parameters measured	Listing thresholds
B. SEMI-FIELD TRIALS		
i)Outdoor applications To determine the dosage of active ingredient per hectare that achieves at least 90% mortality.	Open field assessment with mosquitoes in screen cages, spray vehicle moves through open field.24h mortality	No
ii) Indoor applications To determine the dosage of active ingredient per cubic metre for space treatments that achieves at least 90% mortality.	Empty room assessment with mosquitoes in screen cages and product sprayed through an opening in the wall. 24h mortality	No
C. OPERATIONAL TRIALS		
-To assess effectiveness of the formulated product in operational settings against field populations of the target species.	May be needed in different settings – urban/rural indoor / outdoor etc. Density – the product should achieve 90% relative reduction in density.	90% control should be demonstrated

Characterization of insecticide resistance in tested populations

- New insecticides must be tested against a range of resistant mosquito strains in phase I studies.
- Molecular characterisation of resistance mechanism (target site and metabolic resistance) must be done for tested populations
- In phase II and III, insecticide resistance should be monitored regularly in the wild population by bioassays and, when possible, biochemical or molecular tests.
- In phase II studies, phenotypic resistance should be measured just before the trial or within the 6 months before the trial.
- In phase III studies, phenotypic resistance should be measured before intervention, at the mid-point of the study and at the end of the study.



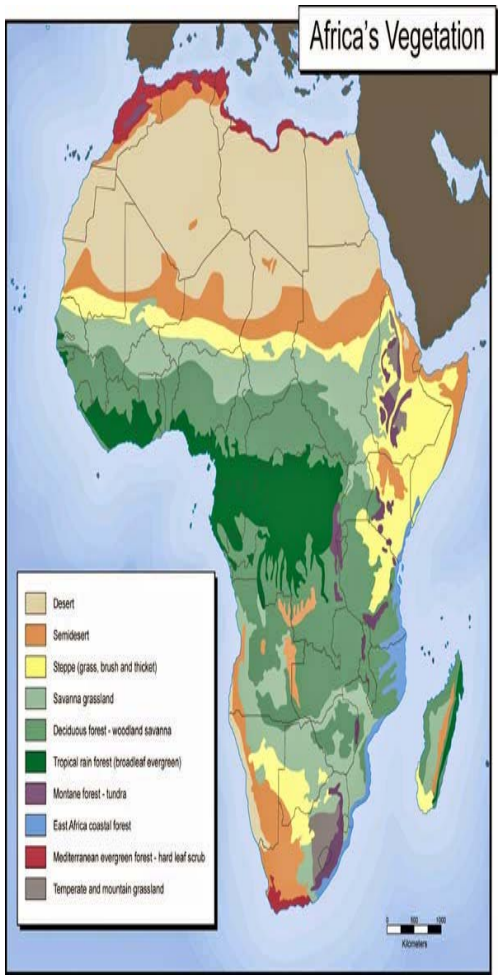


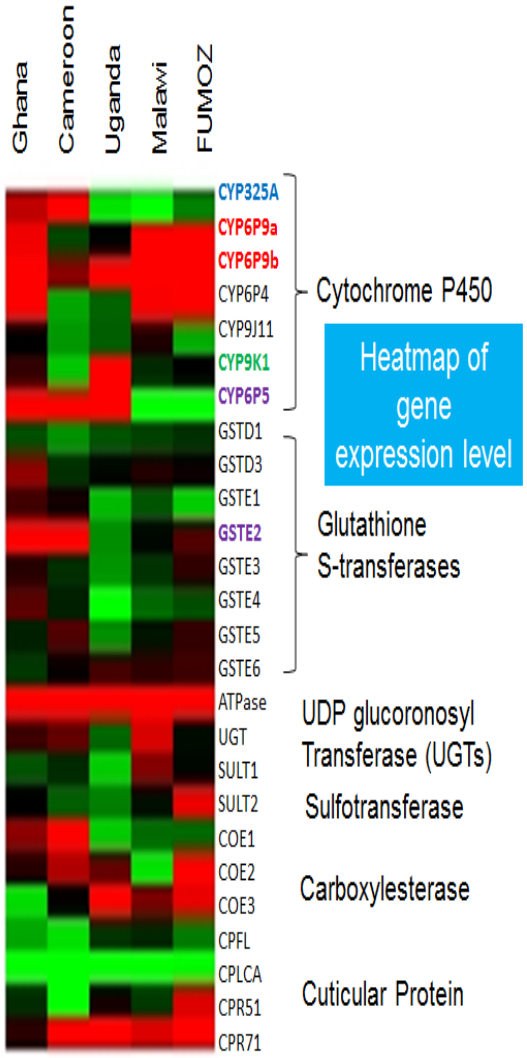
Harris et al 2010

PCR assay Kdr in *Aedes*

Inherent challenges of efficacy testing- Geography

- Geography: Better to include several regions when testing a product since ecological conditions could impact efficacy
- Climate
- Species/Strains

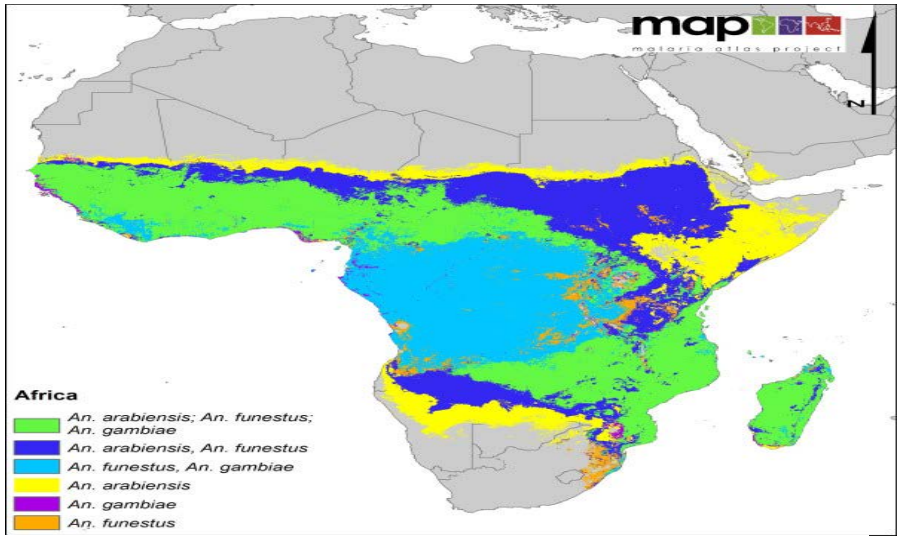


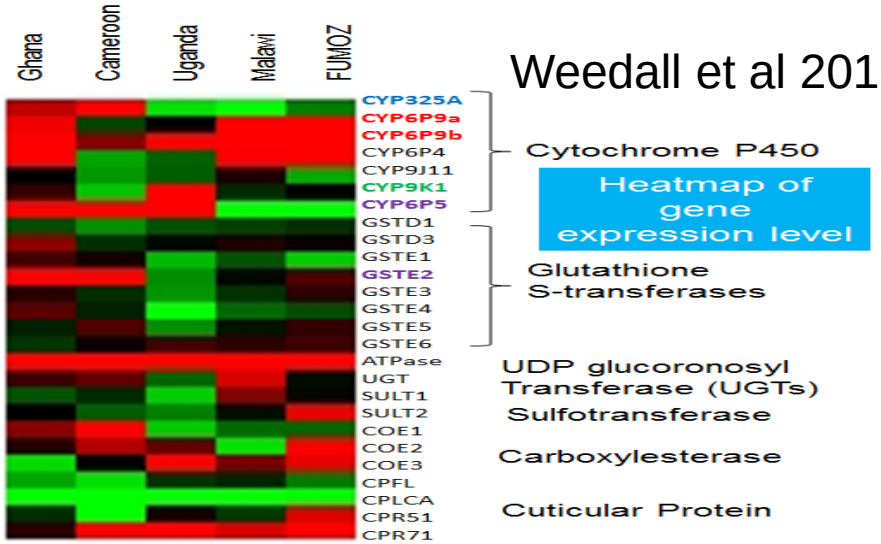


Variation resistance profile in *An. funestus* in Africa

Inherent challenges of efficacy testing- complex vector composition

- Several species
- Some species made of complex of sibling species
- Intraspecific variation e.g for resistance profile and mechanisms variation in same species across Africa





Weedall et al 2018

Key Considerations- Labelling

- The manufacturer is responsible for their label claims, PQT-VC does not propose claims on behalf of the manufacturer

- Example: to claim applicability in various environments, proofs of efficacy in those environments needs to be provided. e.g
  - IRS (generic (applicable to all surfaces), mud, wood, cement, thatched roof and walls, other surface types)
  - Larvicide [open Water (polluted and/or clean water; flowing or stagnant water), Containers, Human and animal consumption risk
  - Space Spray (Indoor, Outdoor, Timing (e.g early morning or late afternoon)
  - Skin Applied Repellent
    - Duration of efficacy
    - Use (outdoor/indoor)

Key Considerations: Importance of species selection and characterization

- What work for mosquitoes does not necessarily for blackflies

- Action of a product on Malaria vectors does not automatically imply action on arbovirus vectors (*Aedes*)

- So need to characterise the various species before claiming efficacy

Key Considerations: Statistical Analysis – Best Practices and presentation of analysis

- Studies must followed recommended statistical tests according to WHO guidelines and must be explained clearly in the study reports
- Need of to follow recommended experimental designs for each study
  - E.g. for LLINs, Latin square rotation of treatments, nets and sleepers
- Lack of statistical analysis will invalidate the study
- E.g. Example of statistical analyses for phase I or Phase II experimental hut studies
  - Non-parametric test, such as the Kruskal-Wallis test, to analyse number of mosquitoes entering a hut etc
  - Logistic regression or generalized linear mixed models used to compare proportion of bloodfed, mortality and exophily between treatments
  - The models should be adjusted for the effects of sleepers and huts.

Assessment

- The DER approach-Data Evaluation Record

- A system set by PQT-VC to compile all information on a specific product from the set of data submitted by the manufacturers
  - All data provided are methodologically assessed using the DER approach with set indicators retrieved from those data to facilitate comparison of reviews and decision-making

- If Variable residual efficacy results, then weight of evidence approach from multiple studies taken into account?

Assessment-DER: Compilation of Information and Interpretation of results

- **1-Identifying Information of the product** (study type, Product name, formulation type date of study etc)
- **2-General Description of Study** (including purpose of study)
- **3-Was the study conducted according to Good Laboratory Practice (GLP) or non-GLP?**
- **4-Description of Study Method (Target pests, application rate, use type (e.g. LLIN, larvicide etc)**
- **5-Results** (record all results; state whether results supported by evidence or not)
- 6-**Reviewer Conclusions on Study:** overall assessment on the quality of the study, adherence to guideline(s), and conclusions on results
- 7-**Label Language Considerations**: Reviewer makes any recommendations for statements to appear on the label based on the assessment

Stage 5 b
Introduction to Inspections

Dr Joey Gouws
PQT Group Lead: Inspections
Regulation of Medicines and other Health Technologies

Dr David Livingstone

” Dr Livingstone, I presume” - Henry Stanley

David Livingstone (1813), British physician, Congregationalist, and pioneer Christian missionary with the London Missionary Society, an explorer in Africa, and one of the most popular British heroes of the late 19th century Victorian era died of malaria in 1873.

becoming the first European to cross the width of southern Africa and changing the western worlds perception of Africa.

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Goodbye Malaria 2013

- Swaziland
- RSA
- Mozambique

Programme

Indoor residual spraying

- 80% houses sprayed
- Effective 3-6 months
- Type of insecticide
- Type of surface

Mosquito nets

Inspections initiated

Inspections contain 2 parts

- **Desk Review**
  - Review of SMF documentation
- **On-site Inspection**

AN ON-SITE INSPECTION IS NOT MANDATORY PRIOR TO PREQUALIFICATION DECISION MAKING

Inspection activities

Objective of the inspection is to assess the facility's ability to provide vector control products that consistently meet the set specifications and applicable requirements.

- Criteria-ISO 9001:2015 Standard
- Inspections started in May 2018
- Inspections conducted in India, Tanzania and Pakistan
- 7 inspections have been conducted to date
- 14 inspections planned to the end of 2018

Inspection Process

- Inspection planning
- Inspection conducting
- Inspection ending
- Inspection report writing
- Evaluate company Corrective and Preventative Action: CAPA
- Close out of inspection

Inspection Planning

- Identify site based on inspection triggers
  - New
  - Routine
  - Complaint
  - Assessment request
- Identify inspection team
- Communication with manufacturer (suitable inspection dates, required documentation)
- Inform Site of the inspection team (Brief CVs provided)
- Provide inspection plan: 1-2 weeks prior to the inspection

Inspection: Conducting

- Opening meeting, end of day discussions, full transparency
- Exchange of information between WHO and Manufacturer
- Inspection and tour of the site-review manufacturing process
- Inspect documents and records
- Sampling process with risk based emphasis
- Review raw data related to the submitted dossier
    - Validation data
    - Stability studies
    - Performance data
- Summarise findings at day end

End of Inspection

- Closing meeting to discuss findings and clarify observations
- A list of findings is left with the manufacturer to allow CAPA preparation
- Write and issue report within 30 days of the site inspection
- Grading of all nonconformities in accordance with ISO
    - Grading independently reviewed prior to release of final report

Inspection report writing

- Write and issue report within 30 days of the site inspection
- Reports are compiled by the lead inspector
- Reports are quality controlled
- Approval and release of the report is by the WHO authorized approver
- Grading of all nonconformities in accordance with ISO
    - Grading independently reviewed prior to release of final report

Corrective and Preventative Action Plan CAPA

- CAPA to be submitted within 30 days of receipt of report
  - Root cause analysis
  - Correction
  - Corrective action to prevent reoccurrence
  - Timeline and responsible person/department
  - Evaluation of the effective implementation of the corrective action
- Normally - two rounds of CAPA are allowed

Close out of Inspection

- Close out letter submitted
- Publish WHO Public Information Report (WHOPIR) in consultation with Manufacturer

Common non-conformances: ISO 2001-2015

Procedures and documentation inadequate –Lack of critical SOP's

- Lack: Quality testing procedures
- Documentation unavailable at site but kept at HQ
- Procedures not readily available to the staff on the floor
- No design or development documents (due to age of products)
- No validation or qualification records for equipment
- Documentation- reports, certification, results not protected from the possibility of alteration or change

People inadequate

- Quality policy not communicated within the facility
- Inadequate Personal Protection
- Training inadequate

Common non-conformances: ISO 2001-2015 …cont

Premises inadequate

- QC Laboratory facility is basic with areas require improvement.

Processes inadequate

- Inadequate traceability of the products at all stages of production with info limited and uninformative
  - containers relabelled with a unique number or identifier but no reference to regulatory requirements:
    - batch numbers
    - expiry dates
    - storage requirements etc.
  - information in the BMR not referable to QC testing results.
- Cleaning: Reactors and large scale vessels
    - Inadequate cleaning when changing from one process to another

Way forward

Open door policy

- New area: WHO and Industry
- Transparency
- Mutual trust: WHO and Industry
- Willingness to address challenges
- Adopt a common problem solving attitude
- Knowledgeable: Tap into PQT experience and lessons learnt

Joey Gouws
PQT: Group Lead Inspections
Regulation of Medicines and other Health Technologies
gouwsj@who.int

Thank you

End Scene – Preparations for Stage 6 in progress .....

Stage 6: Decision Making

Decision making is a process

- Compilation of summaries by discipline leads and case managers
- Drafting of decision document
- Presentation to management of the key findings and points of interest
- Sharing of draft decision document with applicant for error correction
- Finalization of the decision document

Science Management Meetings

- Scheduled for PQT-VC management and staff to discuss key issues with experts

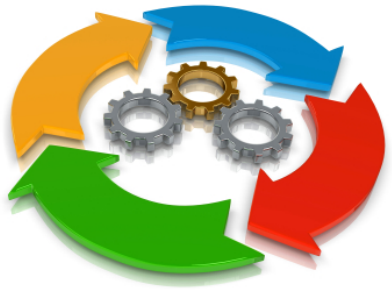
Listing of Prequalified Products

- Applicant and Product Attributes
- Manufacturing Sites
  - WHO Public Inspection Reports
- Letter of Prequalification
- Decision Document
- Declaration of Labelling
- Supporting Specification

End Scene – Preparations for Stage 7 in progress .....

Stage 7: Post-Prequalification Activities

Post-Prequalification Activities



- Addressing post-prequalification commitments
- Post PQ Changes
- Complaints
- Re-inspection

- Products may be suspended or delisted for failure to comply with stipulated requirements

Addressing post-prequalification commitments

- PQ Listing Decisions may include requirements for additional information to be submitted
- Such requirements will be discussed with the applicant prior to the finalization of the decision

Post PQ Changes (PPQC)

Service Code	Service
PQ500	Post PQ Change: Major
PQ501	Post PQ Change: Minor

- Request meeting if clarity needed
- Compile application
  - WHO PQT-VC Post-PQ Change Application Form
- Submit
- Process for screening and evaluation is the same

Complaints

- Anyone can submit a complaint
- Addressing complaints is a collaborative process with the manufacturer and potentially other stakeholders

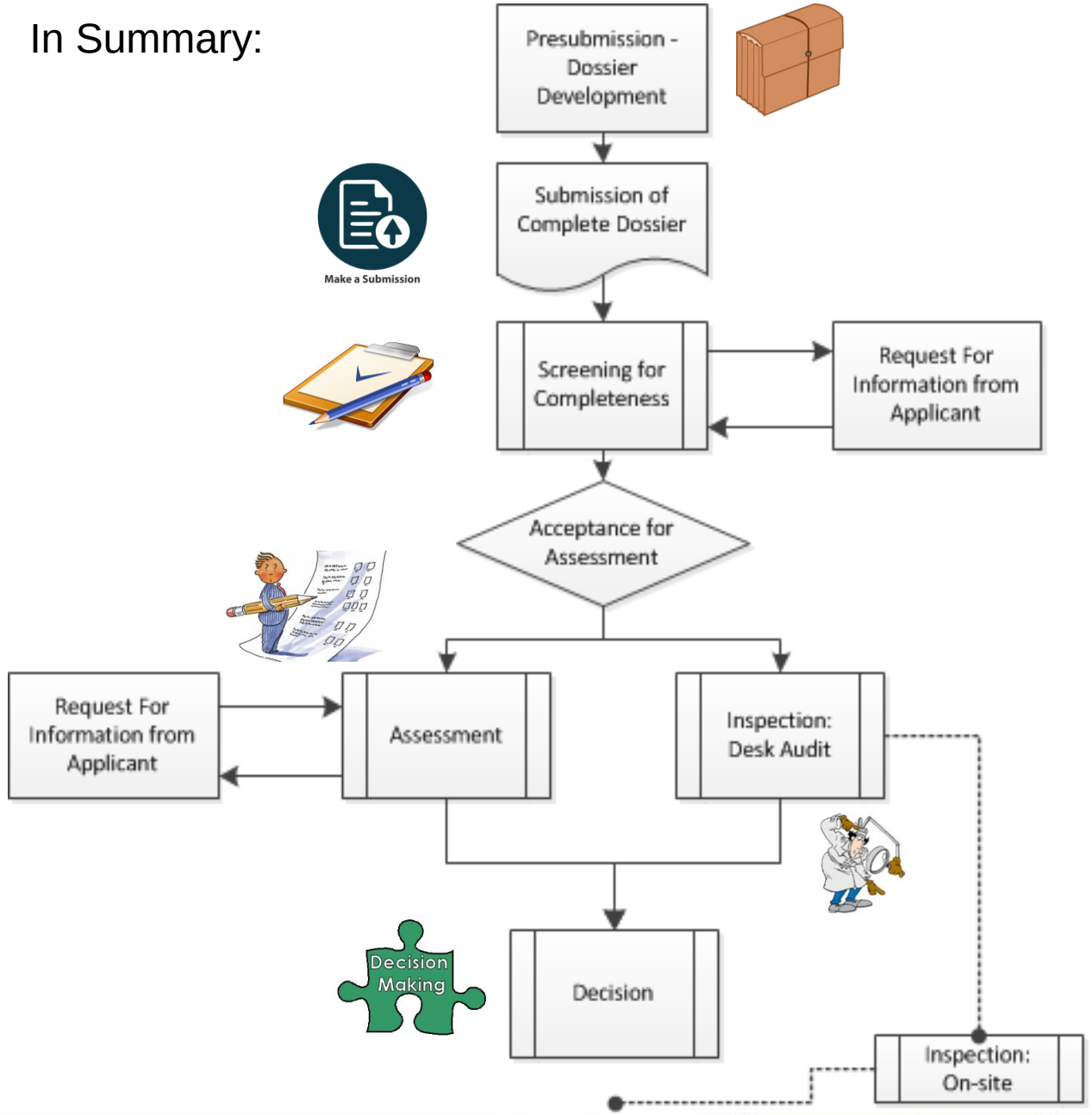
Complaints Process

1. Complaint Logged
2. Complaint Validated
3. Correction Identified
4. Correction Implemented
5. Root Cause Identified
6. Corrective Action Identified
7. Corrective Action Implemented
8. Corrective Action Effectiveness Checked

Re-inspection

- Criteria and timelines for re-inspection are under development

In Summary:


Presubmission - Dossier Development
Make a Submission
Submission of Complete Dossier
Screening for Completeness
Request For Information from Applicant
Acceptance for Assessment
Request For Information from Applicant
Assessment
Inspection: Desk Audit
Decision Making
Decision
Inspection: On-site

End Play – A collective sigh of relief