

# METHODS AND TECHNIQUES FOR ASSESSING EXPOSURE TO ANTIMALARIAL DRUGS IN CLINICAL FIELD STUDIES

INFORMAL CONSULTATION ORGANIZED BY THE WORLD HEALTH ORGANIZATION WITH THE TECHNICAL SUPPORT OF THE WORLDWIDE ANTIMALARIAL RESISTANCE NETWORK

22-24 FEBRUARY 2010, BANGKOK, THAILAND





WHO Library Cataloguing-in-Publication Data:

Methods and techniques for assessing exposure to antimalarial drugs in clinical field studies.

1.Antimalarials - blood. 2.Antimalarials - therapeutic use. 3.Antimalarials - pharmacokinetics. 4.Artemisinins - therapeutic use. 5.Malaria - drug therapy. I.World Health Organization. II.Informal consultation organized by the World Health Organization with the technical support of the worldwide antimalarial resistance network.

ISBN 978 92 4 150206 1

(NLM classification: OV 256)

### © World Health Organization 2011

All rights reserved. Publications of the World Health Organization are available on the WHO web site (www.who.int) or can be purchased from WHO Press, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland (tel.: +41 22 791 3264; fax: +41 22 791 4857; e-mail: bookorders@who.int). Requests for permission to reproduce or translate WHO publications – whether for sale or for noncommercial distribution – should be addressed to WHO Press through the WHO web site (http://www.who.int/about/licensing/copyright\_form/en/index.html).

The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

All reasonable precautions have been taken by the World Health Organization to verify the information contained in this publication. However, the published material is being distributed without warranty of any kind, either expressed or implied. The responsibility for the interpretation and use of the material lies with the reader. In no event shall the World Health Organization be liable for damages arising from its use.

This publication contains the report of an informal consultation and does not necessarily represent the decisions or policies of the World Health Organization.

Editing: Elisabeth Heseltine

Design: elfiga.ch

Layout coordination: Claudia Corazzola, WHO Graphics

Cover: Denis Meissner, WHO Graphics

Printed in France

Contents 3

# **Contents**

Acknowledgements 5 Abbreviations 6						
Chapter 1.		11				
1.1	Overview	11				
1.3	Sample preparation Measurement	12 14				
1.4	Methods for measuring antimalarial drug concentrations	20				
1.5	Recommendations	21				
1.6	Rationale	23				
	Assay conditions for measuring antimalarial	20				
Appoilaix 1.	agents in various matrices	25				
_						
Chapter 2.						
Pre-analyt	ical variables in antimalarial drug assays	41				
2.1	Overview	41				
2.2	Biological matrices	41				
2.3	Sampling containers	42				
2.4	Food intake	42				
2.5	Anticoagulants and stabilizers	42				
2.6	Haemolysis	43				
2.7	Drug concentrations in different matrices	43				
2.8	Transport and storage of samples to maintain stability	51				
2.9	Recommendations	57				
2.10	Rationale	59				
Chapter 3.						
<b>Optimizing</b>	sampling schemes for pharmacokinetics studies	61				
3.1	Clinical indications for measuring antimalarial drug concentrations in blood	61				
3.2	Covariates that affect the pharmacokinetics	60				
3.3	of antimalarial drugs Sampling schemes for pharmacokinetics studies	68 70				
3.4	Optimal design methods	70				
3.5	Simplified measurement of exposure to a drug	73				
3.6	Recommendations for intensive strategies	75				
3.7	Recommendations for population pharmacokinetics	13				
<b>-</b> 11	strategies	78				

List of participants		161
References		
5.11	Rationale	128
5.10	Recommendations	127
5.9	Equipment verification	127
5.8	Data archiving	127
5.7	Final analytical reports	126
5.6	Examples of bioanalytical study records	125
5.5	Bioanalytical record-keeping and reports	123
5.4	Benefit of external quality assurance schemes	122
5.3	Corrective action requests	121
5.2	Timing of sample re-analysis	121
5.1	Acceptance criteria in routine analysis	117
of clinical	samples	117
Implement	ation of methods for the analysis	
Chapter 5.		
4.17	Rationale	116
4.16	Recommendations	112
4.15	Dried blood spots	111
4.14	Incurred sample re-analysis	110
4.13	Validation aspects of mass spectrometric assays	109
4.12	Haemolysis and lipaemia	108
4.11	Carryover	108
4.10	Stability studies	105
4.9	Recovery	104
4.8	Sensitivity	104
4.7	Selectivity	104
4.6	Linearity and range	103
4.5	Accuracy and precision	102
4.4	Preparation of standards and quality controls	101
4.3	Standard reference material	100
4.2	Types of method validation	98
4.1	Validation according to international guidelines	95
Validation		95
Chapter 4.		
	pharmaconnected stadies of antimatarial arage	01
Appendix 2.	pharmacokinetics studies of antimalarial drugs	81
Annendiy 2	of drug exposure Suggested sampling windows for population	80
3.10	Rationale for recommended simplified measurement	0.0
0.40	of exposure to antimalarial drugs	80
3.9	Recommendations for simplified measurement	
3.8	Rationale for suggested time windows	80

Acknowledgements 5

# **Acknowledgements**

This technical guidance document would not have been possible without the experience and knowledge of Niklas Lindegardh, who coordinated the consensus meeting and contributed to all parts of the document. Jennifer Norman served as the rapporteur for the meeting and compiled the guidance.

The following contributed to the document as lead writers, contributing writers and peer reviewers:

**Chapter 1:** William Watkins (Chair), Fraction Dzinjalamala, Michael Green, Michael Kozar

**Chapter 2:** Yngve Bergqvist (Chair), Grace Sola Gbotosho, Vincent Jullien, Kesara Na-Bangchang

**Chapter 3:** Julie Simpson (Chair), Michael Ashton, Karen Barnes, Kasia Stepniewska, Joel Tarning, Nicholas White

**Chapter 4:** Niklas Lindegardh (Chair), Michael Douglas Edstein, Lawrence Fleckenstein, Stephen Ward

**Chapter 5:** Peter John Smith (Chair), Michael Douglas Edstein, Jennifer Norman, Lubbe Joachim Wiesner

The following contributed to the consensus discussions and reviewed the final document: Nicholas Day, Arjen Dondorp, Philippe Guérin, Warunee Hanpithakpong, Thomas Kanyok, Qigui Li, Sharif Mahsufi Mansor, Myaing Myaing Nyunt, Gerson Pianetti, Pascal Ringwald, David Saunders, Paktiya Teja-Isavadharm.

Acknowledgments are also due to the Bill & Melinda Gates Foundation for its financial support towards convening the consensus meeting.

### For more information, please contact:

Dr Pascal Ringwald Drug Resistance and Containment Unit Global Malaria Programme World Health Organization 20 avenue Appia 1211 Geneva 27 Switzerland

Tel.: +41 22 791 3469 Fax: +41 22 791 4824

E-mail: ringwaldp@who.int

## **Abbreviations**

AUC area under the concentration–time curve

DBS dried blood spot

EDTA ethylenediaminetetraacetic acid

HPLC high-performance liquid chromatography

ISR incurred sample re-analysis
LC liquid chromatography
LLOQ lower limit of quantification

MS mass spectrometry

MS/MS tandem mass spectrometry

PK pharmacokinetics RBC red blood cell

ULOQ upper limit of quantification

UV ultraviolet radiation

WHO World Health Organization

预览已结束, 完整报告链接和

https://www.yunbaogao.cn/report/index/report?r