

## **Good Formulation Practices for ACTs: Report on Training for Local Manufacturers, Accra, Ghana, August 12, 2005**

---

Gladys Tetteh  
Ben Botwe

Printed December 2006



---

Rational Pharmaceutical Management Plus  
Center for Pharmaceutical Management  
Management Sciences for Health  
4301 N. Fairfax Drive, Suite 400  
Arlington, VA 22203  
Phone: 703-524-6575  
Fax: 703-524-7898  
E-mail: [rpmpplus@msh.org](mailto:rpmpplus@msh.org)

Strategic Objective 5

This report was made possible through support provided by the U.S. Agency for International Development, under the terms of Cooperative Agreement Number HRN-A-00-00-00016-00. The opinions expressed herein are those of the authors and do not necessarily reflect the views of the U.S. Agency for International Development.

## **About RPM Plus**

RPM Plus works in more than 20 developing and transitional countries to provide technical assistance to strengthen pharmaceutical and health commodity management systems. The program offers technical guidance and assists in strategy development and program implementation both in improving the availability of health commodities—pharmaceuticals, vaccines, supplies, and basic medical equipment—of assured quality for maternal and child health, HIV/AIDS, infectious diseases, and family planning and in promoting the appropriate use of health commodities in the public and private sectors.

## **Recommended Citation**

This report may be reproduced if credit is given to RPM Plus. Please use the following citation.

Tetteh, G, and B. Botwe. 2006. *Good Formulation Practices for ACTs: Report on Training for Local Manufacturers, Accra, Ghana, August 12, 2005*. Submitted to the U.S. Agency for International Development by the Rational Pharmaceutical Management Plus Program. Arlington, VA: Management Sciences for Health.

Rational Pharmaceutical Management Plus Program  
Management Sciences for Health  
4301 North Fairfax Drive, Suite 400  
Arlington, VA 22203 USA  
Telephone: 703-524-6575  
Fax: 703-524-7898  
E-mail: [rpmpplus@msh.org](mailto:rpmpplus@msh.org)  
Web: [www.msh.org/rpmpplus](http://www.msh.org/rpmpplus)

## CONTENTS

ACRONYMS AND ABBREVIATIONS .....	v
EXECUTIVE SUMMARY .....	1
BACKGROUND .....	3
Introduction.....	3
Local Production of Medicines in Ghana .....	4
Establishment of a Quality Assurance Program .....	5
Rationale for Good Formulation Practices Training.....	7
PROCEEDINGS OF THE GOOD FORMULATION PRACTICES TRAINING.....	9
Workshop Participants .....	9
Workshop Presentations.....	10
WORKSHOP RECOMMENDATIONS AND CONCLUSIONS.....	13
ANNEX 1. WORKSHOP AGENDA .....	15
ANNEX 2. PRESENTATIONS.....	17



## ACRONYMS AND ABBREVIATIONS

ACT	artemisinin-based combination therapy
API	active pharmaceutical ingredient
FDB	Food and Drugs Board
Global Fund	Global Fund to Fight AIDS, Tuberculosis and Malaria
GMP	Good Manufacturing Practices
IM	intramuscular
INN	international nonproprietary name
IPTp	intermittent preventive treatment in pregnancy
IV	intravenous
MSH	Management Sciences for Health
NMCP	National Malaria Control Programme
RPM Plus	Rational Pharmaceutical Management Plus Program
SP	sulfadoxine-pyrimethamine
USAID	U.S. Agency for International Development
USP	United States Pharmacopeia
WHO	World Health Organization



## EXECUTIVE SUMMARY

Ghana changed its malaria treatment policy in 2004 to include the use of an artemisinin-based combination therapy (ACT) as first-line treatment for uncomplicated malaria. The selected ACT for first-line treatment is co-packaged artesunate + amodiaquine, which is procured largely through financing from a Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM or Global Fund) Round 4 grant. To ensure the availability of the recommended ACT, the local manufacture and co-packaging of artesunate and amodiaquine have been encouraged by the Ministry of Health of Ghana. To ensure the production of high-quality, locally manufactured ACTs, a quality assurance program for the selected artesunate/amodiaquine combination was instituted within the Food and Drugs Board (FDB), establishing guiding principles for manufacturers.

As part of preparations for ACT policy implementation, an assessment of the quality of available malaria medicines on the Ghanaian market was conducted in July 2004 by the Management Sciences for Health (MSH) Rational Pharmaceutical Management (RPM) Plus Program, in conjunction with the Ghana National Malaria Control Programme (NMCP) and FDB. The aims of the assessment were both to gather information to determine the quality of malaria medicines on the market and to recommend interventions that would prepare the way for importation of raw products and local manufacture of ACTs.

The assessment found important quality deficiencies in antimalarials sampled from the market. Recommendations made to address the assessment findings were (1) to improve pharmaceutical management; (2) to strengthen necessary regulatory measures needed to maintain the high quality of antimalarials; and (3) to train pharmaceutical companies in Ghana on good formulation practices.

In August 2005, the FDB organized a one-day workshop targeting quality control and production managers of all pharmaceutical companies in Ghana. The workshop, held at the Kama Conference Centre in Accra, was funded by the Ghana Mission of the U.S. Agency for International Development (USAID) through the RPM Plus Program of MSH. The workshop was aimed at equipping local manufacturers in Ghana with the requisite skills for formulation of ACTs and was expected to encourage manufacturers to—

1. Ensure that local ACTs are produced according to good formulation practices
2. Produce high-quality and efficacious medicines
3. Be responsible for the quality of their products throughout the distribution chain

A total number of 12 local manufacturing companies were represented at the training by two representatives each (quality control manager and production manager). Other stakeholders present at the meeting were representatives of the Ghana country office of the World Health Organization's Department of Essential Drugs and Medicines Policy, the NMCP, and RPM Plus.

By the end of the workshop, it was clear that company representatives present had been equipped with the skills of good formulation methods, to support the objective of producing high-quality

products. The training was seen as timely by stakeholders. The general consensus was that the workshop would provide a good basis for local ACT manufacturers to adopt good formulation practices.

## BACKGROUND

### Introduction

The emergence and spread of *Plasmodium falciparum* resistance to chloroquine led Ghana to change its malaria treatment policy in 2004 to include the use of an artemisinin-based combination therapy (ACT) as first-line treatment for uncomplicated malaria. Previously, chloroquine was Ghana's first-line therapy for the treatment of uncomplicated malaria, and sulfadoxine-pyrimethamine (SP) was used as second-line therapy. Currently, Ghana recommends artesunate + amodiaquine for the treatment of uncomplicated malaria and is implementing its new malaria treatment policy, which includes the use of SP for intermittent preventive treatment in pregnancy (IPTp)<sup>1</sup>. The policy is summarized in Table 1.

**Table 1. Ghana Antimalarial Treatment Policy**

Condition	Recommendation	Dosage Form	Strength
Uncomplicated malaria (first-line treatment)	Artesunate + amodiaquine	Tablet	75 mg artesunate + 150 mg amodiaquine
Uncomplicated malaria (second-line treatment)	Quinine	Tablet	300 mg
Severe and complicated malaria	Quinine	Injection (IV or IM)	300 mg/ml in 2 ml ampoule
Prevention of malaria in pregnancy	IPTp using SP	Tablet	500 mg sulfadoxine + 25 mg pyrimethamine
Treatment of uncomplicated malaria in pregnancy	Trimester 1: quinine	Tablet	300 mg
	Trimesters 2 and 3: quinine or artesunate + amodiaquine	Tablet	300 mg
		Tablet	75 mg artesunate + 150 mg amodiaquine
Treatment of complicated malaria in pregnancy	The same as the treatment of severe malaria for the general population	NA	NA

Note: NA = not applicable.

Financing for implementing this policy and for purchasing the recommended ACTs has largely been through Global Fund Round 4 grants, with additional funds from the Government of Ghana and the Health Fund.<sup>2</sup> To ensure sustainability, the local manufacture and co-packaging of artesunate and amodiaquine have been encouraged by the Ministry of Health.

<sup>1</sup> Ghana Health Service. 2004. *Antimalarial Drug Policy for Ghana*. Accra: Government of Ghana.

<sup>2</sup> As part of Ghana's sector-wide approach (SWaP), the MOH has created the national Health Fund (account), to which a selected number of partners contribute annually to support the health sector program.

## **Local Production of Medicines in Ghana**

In Ghana, the local practice of pharmacy has always incorporated some elements of manufacturing.<sup>3</sup> As far back as the 1950s, pharmacies both in the government and private sector were known to prepare liquid mixtures such as antacids, cough medicines, and antiseptic lotions; since the 1960s, hospital-based procedures such as ampoule filling and closing have been instituted. Formulations manufactured by GIHOC Pharmaceuticals, initially a state-owned concern comprising 16 companies, include pethidine, diazepam, chloroquine, intravenous infusions, and tablets (paracetamol, chloroquine, and diazepam). Private sector companies, affiliates of foreign companies, such as JL Morrison Son & Jones Ltd., Sterling Products Ltd., Dannex Ltd., Major & Co. Manufacturing, and PZ Industries, also started local manufacture of medicines in the 1960s, with indigenous companies—Ayrton Drug Manufacturing, Namco Ltd., and others—entering the industry in the late 1960s and early 1970s.

The local production of antimalarials under the previous malaria treatment policy—including chloroquine, SP, and quinine—led to a constant supply of affordable medicines for malaria control. This positive impact of local production was achieved under the guidance of the Food and Drugs Board (FDB), Ghana's drug regulatory agency, through registration of products and manufacturers, inspection and postmarketing surveillance, and price negotiation.

### ***Registration of Products and Manufacturers***

The FDB is responsible for the registration of medicines and food products in Ghana. For the registration of a pharmaceutical product, the product dossier and specified number of samples should be submitted by the manufacturer for evaluation. The dossier should include the generic name of the product and its physicochemical, pharmacological, and toxicological properties. If the product meets the board requirements, the product is registered. To receive approval to manufacture medicines in Ghana, prospective manufacturers must submit to FDB technical plans and drawings as well as a list of items to be manufactured. When the manufacturing premises are ready for production, a Good Manufacturing Practices (GMP) inspection is conducted and a license issued for the commencement of production after a satisfactory report.

### ***Site Inspection and Postmarketing Surveillance of Registered Products***

The FDB inspects manufacturing facilities in the country and conducts workshops to enable companies to maintain and improve their compliance with GMP standards. In addition, the FDB conducts regular postmarketing surveillance of registered pharmaceutical products on the market, and withdraws from the market any product found to be substandard. The manufacturer/agent of the affected product(s) is informed, and then measures are taken to follow through the withdrawal process.

---

<sup>3</sup> Grupper, M., E. Amporful, F. Boateng, and J. Binka. 2005. *Improving Access to Medicines: The Case of Local Production and Greater Access to Medicines for Ghana*. Accra, Ghana: Ministry of Health.

### ***Price Negotiations for Antimalarials on the Essential Medicines List***

The national health insurance scheme mandates affordable pricing of medicines, and the Government of Ghana negotiates prices with suppliers. Stakeholders from the pharmaceutical industry participate in the negotiating team and ensure the inclusion of locally manufactured products within the scheme. Sourcing of active pharmaceutical ingredients (APIs) for local industry must be efficient in order to maintain competitive pricing of locally manufactured products.

### **Establishment of a Quality Assurance Program**

As part of planning for ACT policy implementation, an FDB-run quality assurance program was instituted for the selected artesunate/amodiaquine combination, based on these parameters: screening of APIs, specifications for raw materials and the finished product, and labeling.

#### ***Raw Materials Screening***

Under the quality assurance program, the FDB will screen all the APIs (raw materials) of artesunate and amodiaquine to be used by local companies to manufacture the combination product. The raw materials will be screened for—

- Impurities
- Related substances
- Metals due to catalysts used
- Polymorphism

Required specifications for APIs for the amodiaquine/artesunate combination include—

- Identification
- Water
- Residue on ignition
- Chromatographic purity (related substances)
- Organic volatile impurities (residual solvents)

#### ***Specifications for Finished Products***

All finished batches of amodiaquine/artesunate product must meet these specifications—

- Uniformity of weight of tablets
- Rapid disintegration time
- Dissolution rate of not less than 75 percent (should be dissolved in 30 minutes)
- Assay: should show 90–110 percent of labeled content (artesunate) as amount of dissolved active ingredient specified in the individual monograph

Quality specifications for the finished products must adhere to the official monographs according to which they are manufactured: U.S. Pharmacopeia for amodiaquine, and the Chinese Pharmacopeia and the European Pharmacopeia for artesunate.

### **Specifications for Product Packaging**

For the product name, the generic name *artesunate/amodiaquine tablets* must be used by all manufacturers in Ghana. Where a brand name is also used, the font size of the brand name must be, at most, half that of the generic name and should appear below the generic name on all labeling.

The new combination will be tablets in blister packs, with rigid lines to clearly differentiate the daily doses. Dosages for different age groups will be distinguished by the colors of the outer foil as indicated below in Table 2.

**Table 2. Packaging Requirements by Age and Dosage for Amodiaquine/Artesunate in Ghana**

<b>Age</b>	<b>Dosage</b>		<b>Dosage Form</b>	<b>Color Code for Foil Packaging</b>
Adults (14 and above)	Artesunate 200 mg	Amodiaquine 600 mg as base	Caplets, film coated, elongated or elliptically shaped	Red
7–13	Artesunate 100 mg	Amodiaquine 300 mg as base	Tablets or caplets, round, may be film coated	Blue
1–6	Artesunate 50 mg	Amodiaquine 150 mg as base	Dispersible tablets, round	Pink
Infants <1 year	Artesunate 25 mg	Amodiaquine 75 mg as base	Dispersible tablets, round	Orange

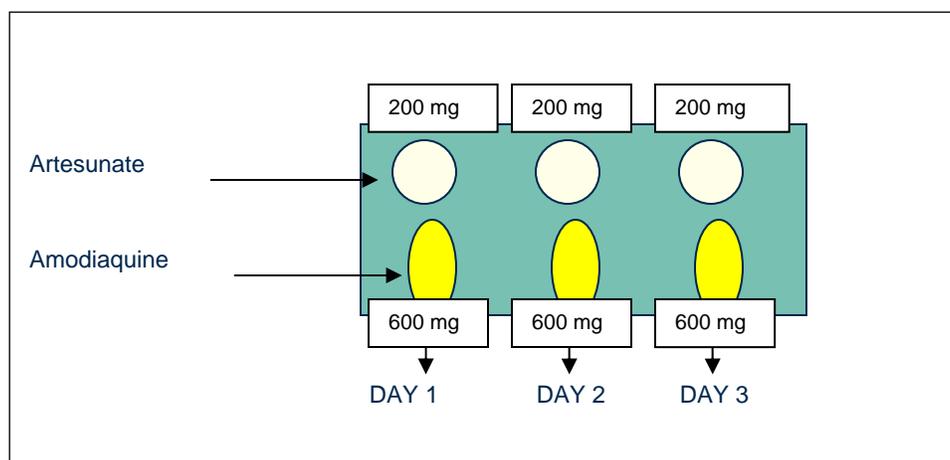
*Note:* The natural colors of artesunate and amodiaquine should be maintained.

### **Labeling**

The FDB recommends that labeling cover two-thirds of the surface area available for the product’s outer packing material. The label should indicate—

1. The name and premise address of the manufacturer
2. International nonproprietary (INN) of all APIs and their respective strengths
3. Indication (s) and dosage
4. Dosage for days 1, 2, and 3, respectively, on the blister pack (Figure 1)

Brand names, if any are used, should appear in type that is no more than half the font size of the generic name.



**Figure 1. Proposed blister packaging indicating dosages for days 1, 2, and 3**

### Rationale for Good Formulation Practices Training

In 2004, during preparation for ACT policy implementation, an assessment of the quality of available antimalarial medicines on the Ghanaian market was conducted by the Rational Pharmaceutical Management (RPM) Plus Program of Management Sciences for Health (MSH), in conjunction with the National Malaria Control Programme (NMCP) and the FDB. The purpose of the assessment was to gather information to determine the quality of antimalarial medicines on the market as well as to recommend interventions to ensure high quality standards for both imported and locally manufactured antimalarials. The assessment revealed important quality deficiencies in sampled antimalarials, and subsequent analysis of samples demonstrated a failure rate of 35.5 percent.<sup>4</sup>

Of 25 samples of SP tested, three samples failed assay testing for sulfadoxine content. All the samples passed assay testing for pyrimethamine content. Four of the 25 samples failed dissolution testing for sulfadoxine, whereas none of the samples failed dissolution testing for pyrimethamine. Of eight amodiaquine hydrochloride samples analyzed, two samples failed assay testing and three failed dissolution testing. A total of 12 artemisinin derivatives were identified as containing their respective active ingredients. However, two of nine artesunate derivatives tested failed assay for API. No artesunate sample failed dissolution testing. The only beta-artemether sample analyzed failed assay testing. Dissolution did not apply to this sample because the product was a soft gelatin capsule. Two dihydroartemisinin tablet forms were analyzed, and one failed dissolution testing.

To address these findings, recommendations were made to improve pharmaceutical management and strengthen regulatory measures needed to maintain high quality of antimalarials, as well as to train pharmaceutical manufacturers in Ghana on good formulation practices. The last

<sup>4</sup> Tetteh, G., B. Botwe, and P. Gyimah. 2006. *Assessment of the Availability and Quality of Antimalarials in the Public and Private Sectors of Ghana* [2005]. Submitted to the U.S. Agency for International Development by the Rational Pharmaceutical Management Plus Program. Arlington, VA: Management Sciences for Health.

intervention would address the problems identified with the dissolution parameters of locally manufactured antimalarials sampled in the assessment.

## PROCEEDINGS OF THE GOOD FORMULATION PRACTICES TRAINING

The FDB organized this one-day workshop for quality control and production managers of all pharmaceutical companies in Ghana on August 12, 2005, at the Kama Conference Centre in Accra. Funding was provided by the USAID/Ghana Mission through the RPM Plus Program of MSH.

The workshop, aimed at equipping local manufacturers in Ghana with the requisite skills for formulation of ACTs, was deemed an important aspect of preparations for implementation of the new malaria treatment policy.

The workshop was expected to encourage manufacturers to—

1. Ensure that local ACTs are produced according to good formulation practices
2. Produce good-quality, efficacious medicines
3. Be responsible for the quality of their products throughout the distribution chain

At the end of the workshop, it was expected that local manufacturers in Ghana would be able to produce antimalarial tablets with the required pharmacokinetic characteristics. In addition, it was expected that the manufacturers would ensure that their products meet the required quality standards.

### Workshop Participants

The FDB invited all current local manufacturers of antimalarials in Ghana as well as prospective local manufacturers of ACTs. The companies present were represented by their quality control and production managers.

A total number of twelve local manufacturing companies were represented at the training by two representatives each (quality control manager and production manager). The companies were—

- Amponsah-Effah Pharmaceuticals Ltd.
- Ayrton Drug Manufacturing
- DanAdams Pharmaceuticals Ltd.
- Dannex Ltd.
- Ernest Chemists Ltd.
- Golden Tower Ltd.
- Kinapharma Ltd.
- LETAP Pharmaceuticals Ltd.
- M&G Pharmaceuticals Ltd.
- Olla Medical Products Ltd.
- Phyto-Riker (GIHOC) Pharmaceuticals Ltd.
- Starwin Products Ltd.

Other stakeholders present at the meeting were representatives of the Ghana office of the World Health Organization's (WHO's) Department of Essential Drugs and Medicines Policy, the Ghana NMCP, and RPM Plus.

## **Workshop Presentations**

Presentation topics were selected with the intention of (1) updating workshop participants on current formulation procedures in accordance with the accepted compendia standards of the FDB; and (2) updating workshop participants on FDB regulatory requirements. The audience was also briefed on global and national malaria treatment policy change processes and issues.

Topics presented and the respective resource persons responsible are described below.

### ***Antimalarial Policy Change, Ms. Naa-Korkor Allotey, NMCP***

Participants were provided with the components of Ghana's former and new malaria treatment policy; the rationale for change; and the importance of producing quality dosage forms in order to prevent the emergence of parasitic strains resistant to ACTs. The NMCP emphasized that the use of the most effective medicines for uncomplicated malaria has the highest potential for reducing morbidity and mortality.

### ***NMCP and the RPM Plus Program, Dr. Gladys Tetteh, MSH***

This presentation highlighted the type of support provided by the RPM Plus Program to malaria control globally and in Ghana. The presentation covered the scope of the malaria problem globally and regionally, challenges, WHO recommendations for first-line treatment, the Abuja targets, the pharmaceutical management cycle, malaria policy change, and pharmaceutical quality control.

### ***Quality Monitoring Project, Mr. Ben Botwe, FDB***

Mr. Botwe, Head of the Drugs Division, FDB, presented the monitoring activities of the board. The board is determined to collaborate with industry to ensure that products entering the market are of the best quality. The board is embarking on strengthening its postmarketing surveillance activities to monitor the quality of ACTs, with the aim of ensuring the health and safety of consumers. Other planned FDB activities include conducting safety monitoring within health institutions, pharmacies, and chemical shops to identify and follow up on possible adverse reactions related to ACTs.

### ***The Chemistry of Artesunate, Amodiaquine, Sulfadoxine, and Pyrimethamine, Mr. Eric K. Boateng, FDB***

This presentation outlined the chemical and physical properties of artesunate, amodiaquine, and pyrimethamine, and how these properties impact formulation, stability, and storage of the respective dosage forms. The challenges involved in the chemical synthesis of the artemisinin

moiety were described. Manufacturers of the SP combination were also cautioned regarding the poor solubility and other physical parameters of sulfadoxine.

### ***Formulation Practices for ACT Dosage Forms, Mr. J. Y. Binka, FDB***

The preformulation factors to consider (i.e., physicochemical factors, including chemical structure, solubility, and spectroscopy), as well as factors altering the performance of medicines, were described in this presentation. Problems associated with formulation and some precautions to be observed during the manufacture of ACTs were also detailed. The presentation also listed and discussed the necessary precautions to be mindful of when procuring APIs. Manufacturers were reminded always to look for the pharmaceutically active forms of API to ensure the production of high-quality ACTs.

### ***Use of Starch and Other Binding & Disintegrating Agents in Tablet Formulation, Dr. S. N. B. Gaizer, DanAdams Pharmaceuticals***

This presentation discussed the chemical and physical properties of starch and other binding/disintegration agents in pharmaceutical formulations. Factors influencing the choice of binding/disintegration agents and the importance of making the right choice were considered.

### ***Specification for the Production of ACTs, Mr. E. Y. Kwarteng, FDB***

Manufacturing companies were asked to adopt specifications recommended by the FDB/NMCP for the production of ACTs for the Ghanaian market. Specifications have been developed under the following broad areas, which were described during the presentation—

- Analytical methods and validation
- Developmental pharmaceuticals and bioavailability
- Bioequivalence and clinical trials
- Specification for stability testing
- Dissolution
- Phase III clinical trials

### ***Requirements for Medicine Registration, Mrs. Deles Darko, FDB***

Participants were reminded of the guidelines for the registration of medicines in Ghana, in accordance with Section 18 of the Food and Drugs Law 1992, P.N.D.C.L 305B, and its amendment, Act 523 1996. Registration requirements and procedures were described, as well the required contents of the product dossier and the SIAMED electronic tool developed by WHO to help countries strengthen implementation of pharmaceutical registration.

### ***Dissolution Testing, Mr. Eric K. Boateng, FDB***

Participants were presented with the history of dissolution testing, including how it has progressed. The significance of dissolution testing and factors influencing the dissolution rate of medicines were discussed. The presenter emphasized medium selection; parameters, including

volume of medium and preparation, type of apparatus and speed, temperature, time, and sampling; filtration; analysis of the samples; and interpretation of results.

## WORKSHOP RECOMMENDATIONS AND CONCLUSIONS

By the end of the workshop, it was clear that company representatives had been equipped with the skills of good formulation methods, with the objective of producing high-quality products. Feedback given during participant discussion demonstrated that the attendees had achieved—

- An appreciation of good formulation practices and their impact on the efficacy of ACTs
- An understanding of the need to produce high-quality medicines that meet safety standards
- Theoretical knowledge of the formulation of tablets with enhanced bioavailability and bioequivalence parameters

The workshop organizers recommended that the FDB conduct routine audit inspections of factories to ensure the proper implementation of the good formulation practices taught. Quality monitoring of locally manufactured ACTs was also agreed upon as a relevant next step. Proposed monitoring would include not only inspection of factory premises but also a nationwide market survey. Under the recommendation, the results of the factory audits and quality monitoring would be analyzed by the FDB to assess the impact of the training program on the quality of ACTs.

The training was seen as timely by stakeholders. The general consensus was that the workshop would provide a good starting point for ACT manufacturers in the country to adopt good formulation practices.



## ANNEX 1. WORKSHOP AGENDA

**Good Formulation Practices Training**  
**Kama Conference Centre, Accra, Ghana**  
**August 12, 2005**

**9.00 a.m.–2.00 p.m.**

<b>Topic</b>	<b>Presenter</b>
ACT policy in Ghana	NMCP, Ms. Naa-Korkor Allotey
Malaria policy change and the quality control of medicines	MSH, Dr. Gladys Tetteh
Specifications for production	FDB, Mr. Ben Botwe
Requirements for registration	FDB, Mrs. Deles Darko
Quality monitoring report	FDB, Mr. Ben Botwe
Formulation practices of ACT dosage forms	FDB, Mr. J. Y. Binka
Use of starch, other disintegrants, and binding agents	DanAdams Pharmaceuticals, Dr. S. N. B. Gaizer
Dissolution testing	FDB, Mr. Eric K. Boateng



## ANNEX 2. PRESENTATIONS

### Antimalarial Policy Change, Ms. Naa-Korkor Allotey, NMCP



# THE NEW ANTI-MALARIAL DRUG POLICY

---

MEETING WITH LOCAL MANUFACTURERS  
by  
Ms. Naa-Korkor Allotey  
NATIONAL MALARIA CONTROL PROGRAMME  
KAMA CONFERENCE CENTRE, ACCRA  
12<sup>th</sup> AUGUST, 2005



## PRESENTATION OUTLINE

- INTRODUCTION/BURDEN OF DISEASE
- HIGHLIGHTS OF THE OLD ANTI-MALARIAL DRUG POLICY
- HIGHLIGHTS OF THE NEW ANTI-MALARIAL DRUG POLICY
- ISSUES
- CONCLUSION

## INTRODUCTION/BURDEN OF DISEASE (1)

- Since 1985 malaria has remained leading cause of illnesses: 3,400,000 outpatient cases in 2004.
  - About 9,600 every day!
  - 6 malaria cases every minute
- About 970,000 children under five suffer from malaria each year.
  - 2,700 every day!
  - 2 malaria cases every minute!

## INTRODUCTION/BURDEN OF DISEASE (2)

- 17% of all deaths are due to malaria.
- Death in vulnerable groups:
  - Children < 5 yrs: 22% of deaths
  - Pregnant women: 2,000 (9.4% of all deaths in pregnant women): 7 deaths every day!

## HIGHLIGHTS OF THE OLD POLICY DOCUMENT



Malaria Condition	First-Line	Second-Line
Uncomplicated malaria	Chloroquine	Sulfadoxine/ pyrimethamine
Severe and complicated malaria	Quinine	
Chemo-prophylaxis in pregnancy	Chloroquine	



### Policy Change for Treatment of Uncomplicated Malaria

**WHO Recommendation:**  
**preferred choice:**  
**artemisinin-based**  
**combination (ACT)**



## What Is Combination Therapy?

- Anti-malarial combination therapy is the *simultaneous use of two or more blood schizonticidal drugs* with different biochemical targets in the parasite and independent modes of action.
  - Combination therapies can be either *fixed-combination* medicinal products OR
  - Multiple-drug therapy, in which the components are *co-administered* in separate tablets or capsules.



## Combination Therapy (2)

- Artemisinin-based combination therapy (ACT) is an anti-malarial combination therapy with an artemisinin derivative as one component of the combination.



## WHY ARTEMISININ-BASED COMBINATION THERAPY (ACT)?

- ◆ **Artemisinin-based combinations have distinct advantages:**
  - Rapid clinical and parasitological cure
  - No documented parasite resistance currently
  - *Reduced gametocyte carriage rate*
  - Generally well tolerated, with few documented adverse events



## OUR CHOICE OF DRUG: ARTESUNATE/AMODIAQUINE

WHY THIS DRUG?

Characteristic	Chloroquine	Artesunate	Artesunate/ mefloquine	Artesunate/ amodiaquine	Artemether/ lumefantrine
Route of administration	Oral	Oral	Oral	Oral	Oral
Efficacy	Low	High	High	High	High
Compliance	Low	Medium	Low	Low	High
Cost	Very low	Medium	Very high	Low	High
Side effects	Low	Medium	High	Low	Low



## HIGHLIGHTS OF THE NEW ANTI-MALARIAL DRUG POLICY

- ◆ UNCOMPLICATED MALARIA
- ◆ SEVERE MALARIA
- ◆ MALARIA IN PREGNANCY

## Uncomplicated Malaria

		Number of Tablets					
kg	Age	Artesunate 50mg Tablets			Amodiaquine 150mg Tablets		
		Day 1	Day 2	Day 3	Day 1	Day 2	Day 3
5-10	Infant <1 yr	½	½	½	½	½	½
11-24	1-6	1	1	1	1	1	1
24-50	7-13	2	2	2	2	2	2
50+	14+	4	4	4	4	4	4

## Management of Treatment Failure (1)

- Establish whether patient complied with the treatment regimen
- Rule out other common febrile illnesses like ear, nose, throat, or urinary tract infection
- Determine presence/absence of malaria parasites in blood film through microscopy



## Management of Treatment Failure (2)

- If treatment failure is confirmed, treat with oral quinine
- Child dose: 10 mg per kg body weight every 8 hours for 7 days
- Adult dose: 600 mg every 8 hours for 7 days



## Management of Severe Malaria and Complicated Malaria (1): IV, IM, Oral

*Quinine is the drug of choice for treating severe and complicated malaria.*

### IV Administration of Quinine

Quinine hydrochloride, 10 mg/kg body weight of salt (max. 600 mg) IV every 8 hours in 5-10 ml/kg of 4.3% dextrose in 0.18% normal saline or in 5% dextrose over 48 hours.



## Management of Severe Malaria and Complicated Malaria (2)

### *IM Administration of Quinine*

Deep IM injection at a dose of 10 mg/kg body weight of quinine every 8 hours using 100 mg/ml quinine (dilute 2 ml of 600 mg quinine in 4 ml of water for injection or saline)

### *Oral Administration of Quinine*

Oral quinine at 10 mg/kg body weight every 8 hours to complete 7 days of treatment



## MALARIA PREVENTION IN PREGNANCY: INTERMITTENT PREVENTIVE TREATMENT

Sulfadoxine-pyrimethamine (sulfadoxine 500 mg plus pyrimethamine 25 mg) would be reserved for IPT; **at least three doses.**

- First dose: First ANC visit after quickening (after 16 weeks of gestation)
- Second dose: At least 1 month after the first dose
- Third dose: At least 1 month after the second dose



Malaria Prevention in Pregnancy: SP will be administered in three doses to pregnant women as D.O.T.

- SP should not be given to pregnant women with history of hypersensitivity or allergy to sulfa-containing drugs.
- Such women should be encouraged to sleep under ITNs.
- Owing to antagonism between folic acid and SP, folic acid supplementation should be delayed 1 week after SP administration.



## TREATMENT OF MALARIA IN PREGNANT WOMEN

### *Treatment of Pregnant Women with uncomplicated Malaria*

- Artesunate/amodiaquine from 2<sup>nd</sup> trimester  
OR
- Oral quinine: 600 mg every 8 hours for 7 days

***(May give quinine, but MONITOR!!!)***

### *Treatment of Pregnant Women with Severe Malaria*

- Same as the treatment of severe malaria in the general population.



## ISSUES

---

- CONTROLLING INDISCRIMINATE ADVERTS OF DRUGS LABELLED AS ANTI-MALARIALS?
  
- ENSURING COMPLIANCE:
  - TWO DIFFERENT DRUGS AT A TIME?
  - SIDE EFFECTS...?

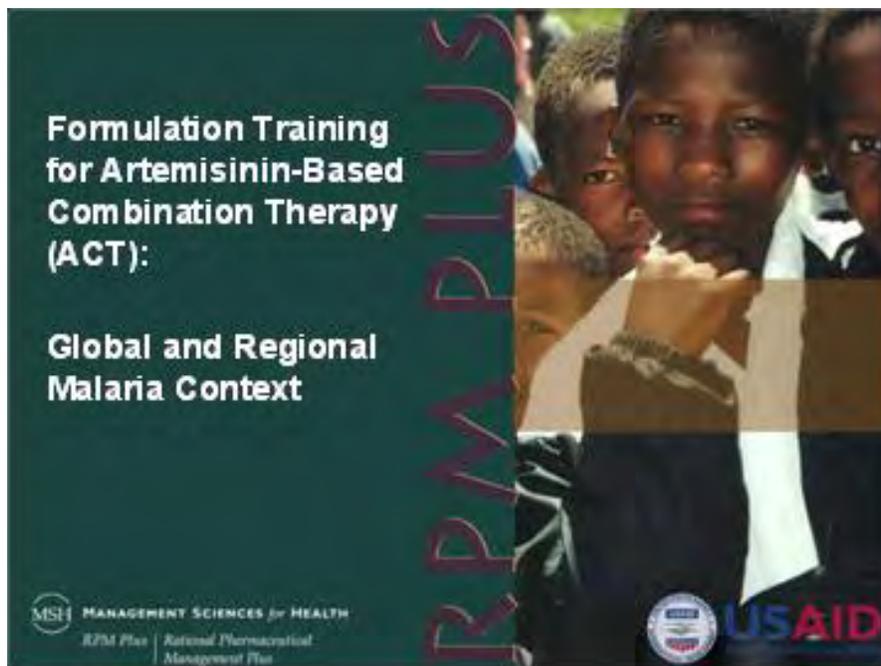
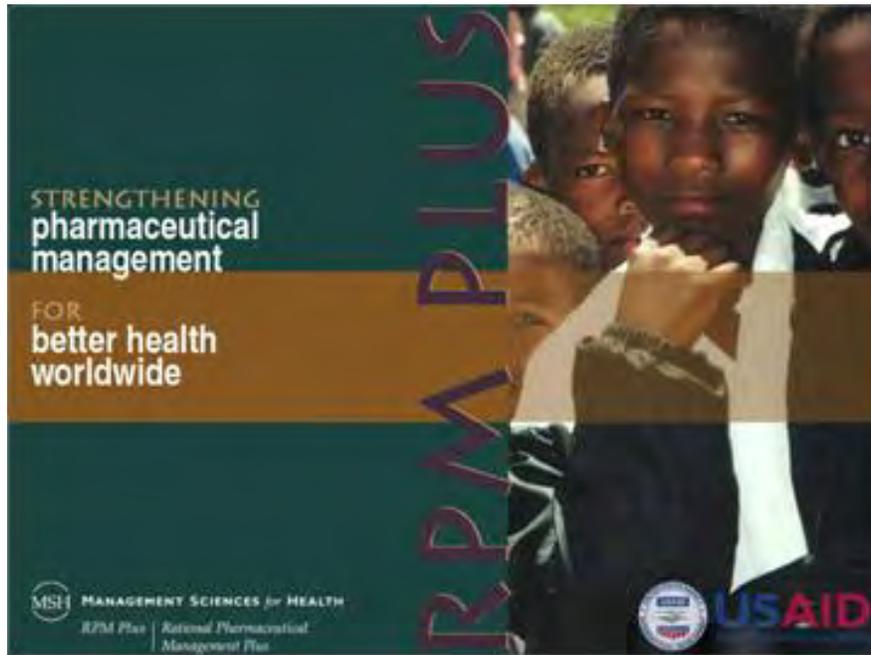


## CONCLUSION

---

- Use of the most effective drug for uncomplicated malaria has the highest potential for reducing morbidity & mortality.

**NMCP and the RPM Plus Program, Dr. Gladys Tetteh, MSH**



## Presentation Outline

- Introduction of RPM Plus
- Scope of malaria problem globally and regionally
- Challenges
- WHO recommendations for first-line treatment
- Abuja targets
- Pharmaceutical Management Cycle
- Malaria policy change and quality control of medicines

## RPM Plus Program

- Rational Pharmaceutical Management Plus  
*Strengthening pharmaceutical management for better health worldwide*
- USAID-funded follow-on program from RPM project
- Awarded in 2000 initially till 2005; now 2008
- Aims to improve management of pharmaceuticals and other essential commodities
- Targets: policy makers, providers, patients, and the public in general

## RPM Plus Work in the Area of Malaria

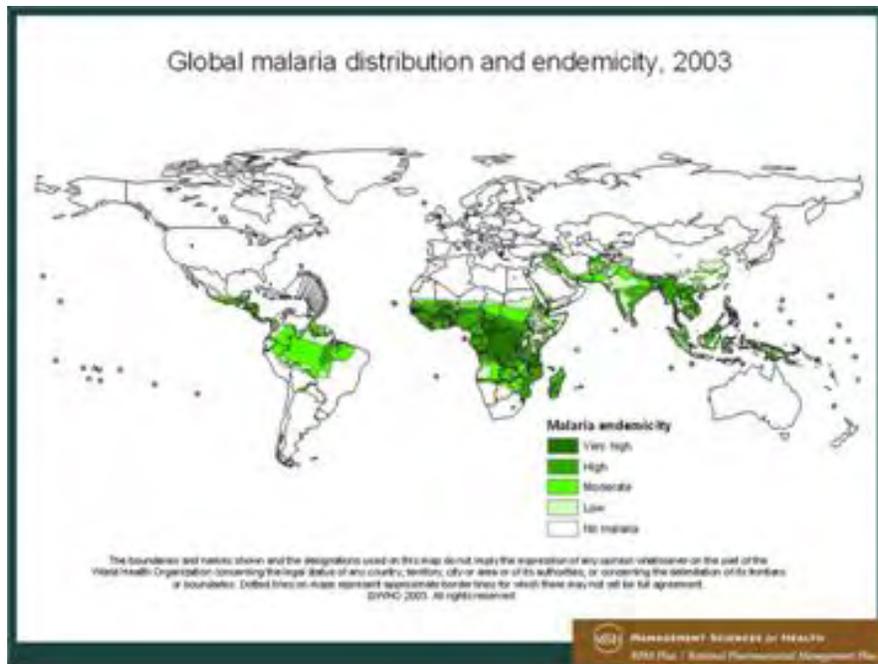
- Engaging in global policy dialogue
- Technical assistance to endemic countries in developing and implementing guidelines
- Strengthening procurement and distribution
- Ensuring rational use
- Developing local capacity to manage antimalarial medicines and commodities
- Work within the Malaria Action Coalition

MSH MANAGEMENT SCIENCES for HEALTH  
RPM Plus | Rational Pharmaceutical Management Plus

## Scope of the Malaria Problem

- Main causes: *P. falciparum*, *P. vivax*
- 300–500 million cases globally annually
- 270–400 million cases of *P. falciparum*
- 40% of the world's population live in areas at risk of malaria transmission (107 countries)
- 70% of cases in Africa, 20% in SE Asia
- In some endemic areas, 40% of outpatients and 50% of inpatients die
- Results from and increases poverty

MSH MANAGEMENT SCIENCES for HEALTH  
RPM Plus | Rational Pharmaceutical Management Plus



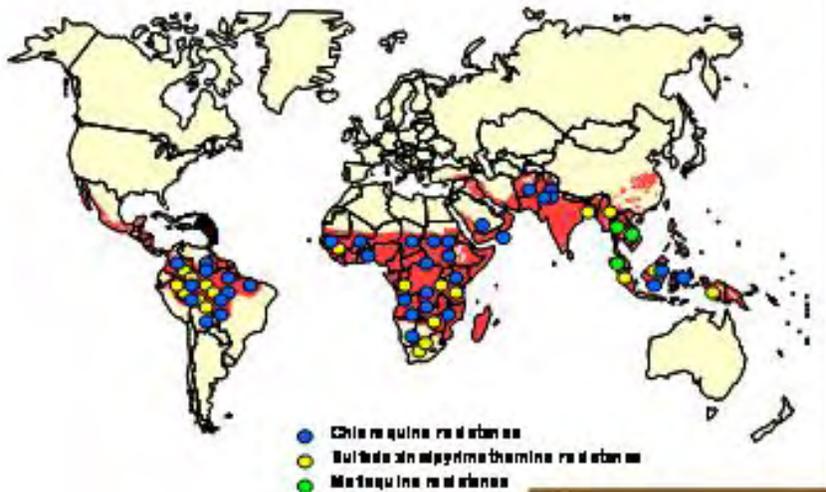
## Malaria in Africa

- Malaria is endemic in 50 countries in sub-Saharan Africa (all countries in SSA except Lesotho)
- *P. falciparum* is the most common cause of malaria in Africa
- Every 30 seconds, a child dies from malaria
- Malaria is the cause of 20% of all deaths in children < 5 years

## Malaria: Challenges

- Growing parasite resistance (*P. falciparum*) to commonly used therapies
- New medicines are more expensive
- Limited experience with new medicines
- Widespread use of the private sector
- Poor-quality/substandard medicines

## Distribution of Drug Resistance



## WHO Recommendations for Antimalarial Treatment

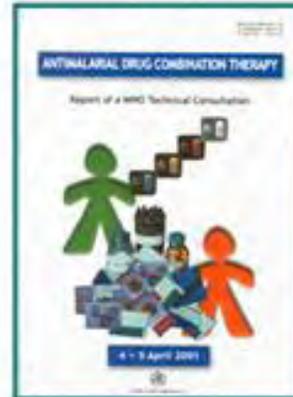
- Each country may have several different treatment recommendations, depending on—
  - Mosquito species
    - *P. falciparum* or *P. vivax*
  - Complications
    - Lab confirmed or not
  - Severity
  - Pregnancy
  - Treatment failure/drug resistance patterns

## Selecting First-Line Antimalarial Medicines (*P. falciparum*) (1)

- All countries needing to change their first-line treatments for *P. falciparum* malaria should change to artemisinin-based combination therapies (ACTs).

## Selecting First-Line Antimalarial Medicines (*P. falciparum*) (2)

- Therapeutic options currently recommended by WHO:
  - Artemether/lumefantrine (fixed-dose combination)
  - Artesunate + amodiaquine
  - Artesunate + sulfadoxine/pyrimethamine (SP) (in areas where SP efficacy remains high)
  - Artesunate + mefloquine (in areas of low transmission)



MSH MANAGEMENT SCIENCES for HEALTH  
RPM Plus | Rational Pharmaceutical Management Plus

## Abuja Targets for Africa (by 2005) (1)

- At least 60% of those suffering from malaria will have access to effective and affordable treatment within 24 hours of the onset of symptoms.



MSH MANAGEMENT SCIENCES for HEALTH  
RPM Plus | Rational Pharmaceutical Management Plus

## Abuja Targets for Africa (by 2005) (2)

- At least 60% of pregnant women who are at risk for malaria, especially those in their first pregnancies, will have access to intermittent preventive treatment (IPT).



MSH MANAGEMENT SCIENCES for HEALTH  
RPM Plus | Rational Pharmaceutical Management Plus

## Abuja Targets for Africa (by 2005) (3)

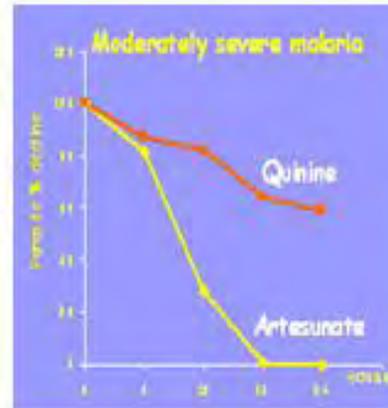
- At least 60% of those at risk for malaria, particularly children under age five and pregnant women, will sleep under insecticide-treated nets.



MSH MANAGEMENT SCIENCES for HEALTH  
RPM Plus | Rational Pharmaceutical Management Plus

## Abuja Targets for Africa (by 2005) (4)

- At least 60% of malaria epidemics will be detected within two weeks of onset and responded to within two weeks of detection.

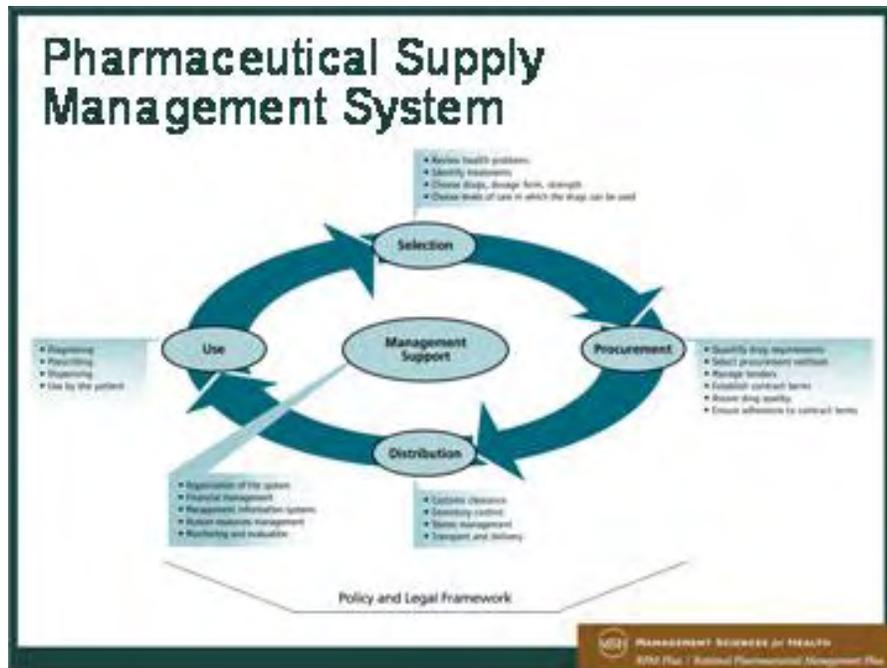


MSH MANAGEMENT SCIENCES for HEALTH  
RPM Plus | Rational Pharmaceutical Management Plus

## Abuja Targets

- Dependent on—
  - Good commodity management
    - Availability of the right commodities (of good quality) at the right time in the right quantities at the right place and taken correctly

MSH MANAGEMENT SCIENCES for HEALTH  
RPM Plus | Rational Pharmaceutical Management Plus



## Malaria Treatment Policy and ACT Quality

- One major goal of policy is to ensure prompt treatment with safe, affordable, and effective medicines.
- The Food and Drugs Board is a major stakeholder in ACT policy implementation.
  - Strives to ensure drug quality, safety, efficacy
  - Operates within the context of existing policies and laws
  - Works closely with the public procurement agency

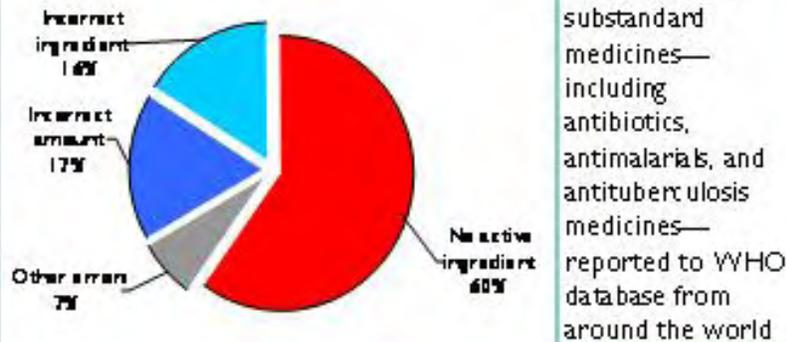
## Definitions of Quality Control and Quality Assurance

- Quality control: The testing of pharmaceutical samples against specific standards of quality
- Quality assurance: The management of activities required to ensure that the pharmaceuticals that reach the patient are safe, effective, and acceptable to the patient

Source: Management Sciences for Health and World Health Organization. 1997. *Managing Drug Supply*. 2d ed. Bloomfield, CT: Kumarian Press. p. 182.

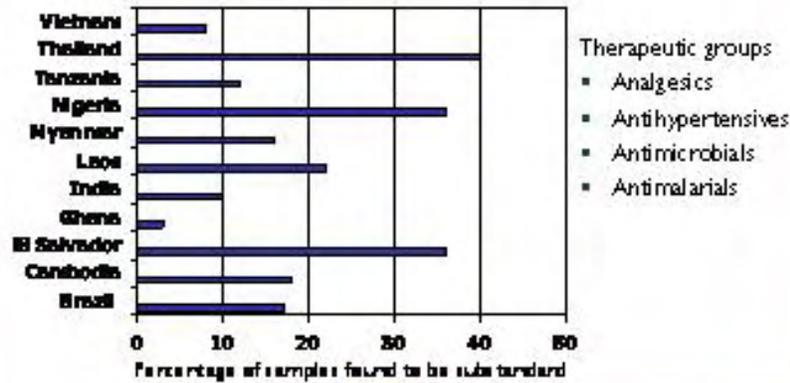
MSH MANAGEMENT SCIENCES for HEALTH  
RPM Plus | Rational Pharmaceutical Management Plus

## Substandard Medicines in Developing Countries (I)



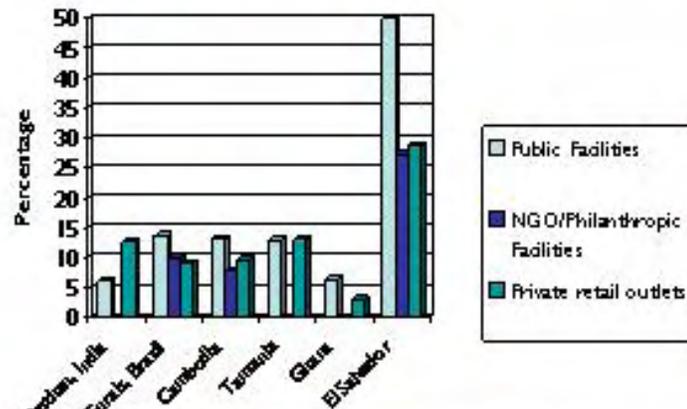
MSH MANAGEMENT SCIENCES for HEALTH  
RPM Plus | Rational Pharmaceutical Management Plus

## Substandard Medicines in Developing Countries (2)



MSH MANAGEMENT SCIENCES for HEALTH  
RPM Plus | Rational Pharmaceutical Management Plus

## Substandard Medicines in Developing Countries (3)



MSH MANAGEMENT SCIENCES for HEALTH  
RPM Plus | Rational Pharmaceutical Management Plus

## Quality in Pharmaceutical Development (1)

- Therapeutic value (documented through clinical trials)
  - Efficacy
  - Safety
- Pharmaceutical product quality (verified through laboratory tests)
  - Product attributes
    - Active pharmaceutical ingredient
    - Dosage form

## Quality in Pharmaceutical Development(2)

- Equivalence of multisource products (established through in vitro and in vivo studies)
  - Bioequivalence

## Determinants of Drug Product Quality

- Drug production
- Equipment and maintenance
- Plant environment
- Manufacturing process
- Quality control
- Drug formulation
- Active ingredients
- Inactive ingredients
- Packaging—immediate and external
- Handling and storage conditions

## Assuring Pharmaceutical Product Quality

### Stakeholders

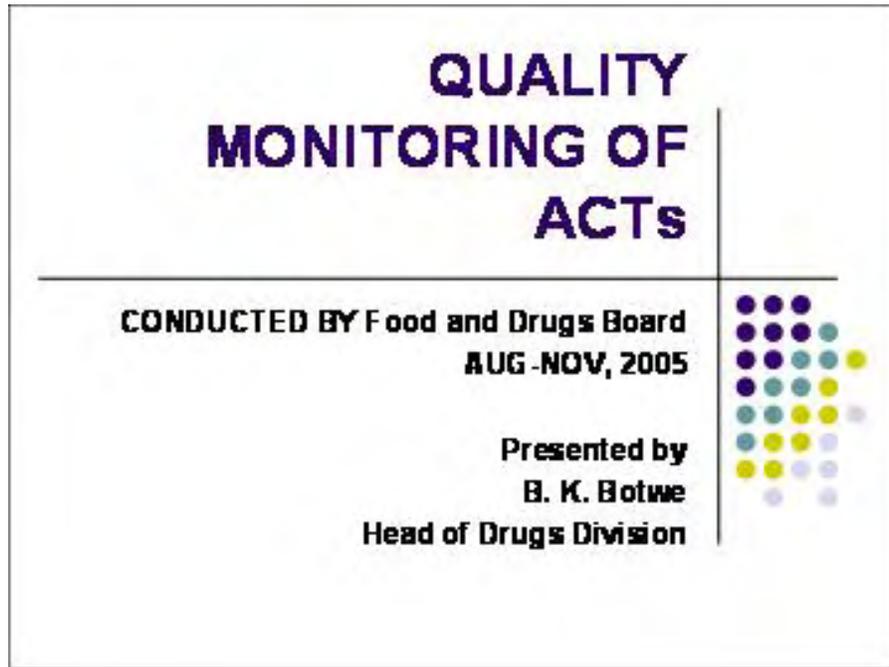
- Drug regulatory authority
- Quality control laboratory
- Procurement agencies
- Local manufacturers
- Pharmaceutical importers
- Port of entry officials
- Pharmaceutical distributors
- Providers
- Patients



## Summary

- Assuring the quality of pharmaceutical products, including ACTs, will require a comprehensive program that involves documentation review, inspection of manufacturing and distribution facilities and products, laboratory testing, reporting and monitoring of product problems, evaluation, and enforcement.

Quality Monitoring Project, Mr. Ben Botwe, FDB

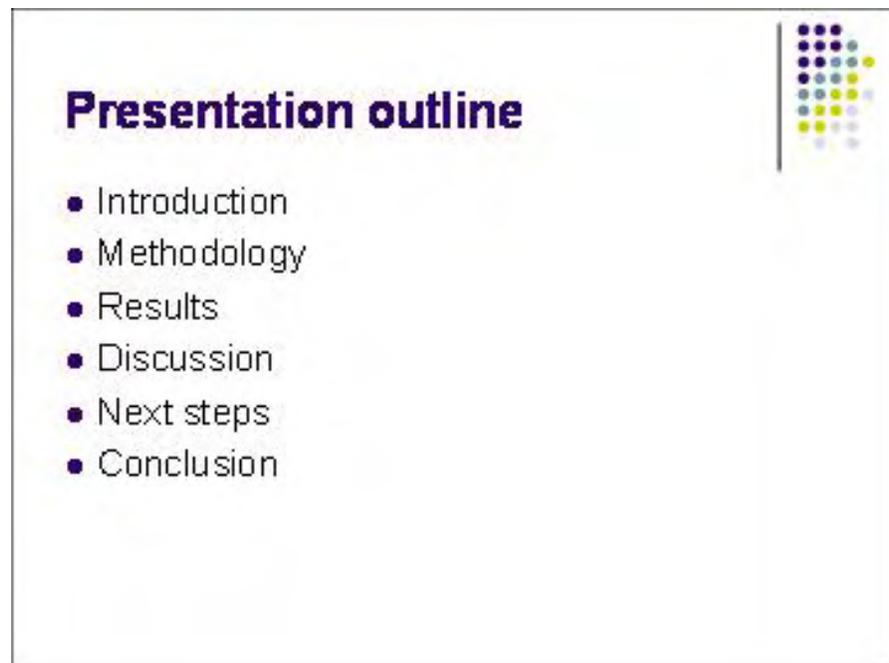


**QUALITY  
MONITORING OF  
ACTs**

---

**CONDUCTED BY Food and Drugs Board  
AUG -NOV, 2005**

**Presented by  
E. K. Botwe  
Head of Drugs Division**



**Presentation outline**

- Introduction
- Methodology
- Results
- Discussion
- Next steps
- Conclusion



## **Introduction**



- Policy change for treatment of uncomplicated Malaria
- WHO recommended artemisinin-based combination (ACT)
- Artesunate-Amodiaquine combination adopted as the first line treatment for malarial by MOH
- Board mandated by National Malaria Control Program to monitor quality of ACT's on the market

## **Methodology**



### **Study design & Sampling**

- Five (5) out of Ten (10) regions were selected
  - Greater Accra
  - Ashanti
  - Eastern
  - Volta
  - Western

## Methodology contd.



- Samples bought from pharmacies and licensed chemical shops clinics and hospitals in the regional capitals
- Total of 41 samples procured
- Preliminary labelling and packaging evaluation was conducted
- A sampling sheet developed to facilitate exercise
- Samples sent to FDB QCL for analysis

## Methodology contd.



### Analytical Methods

- Samples were analyzed according to the
  - USP/NF 28, 2005 for Amodiaquine
  - IP volume 5 page 193-225 for the Artemisinin derivatives:
    - Artesunate
    - Dihydroartemisinin

## Methodology contd.



### Test were on:

- Identification of product and physical appearance
- Dissolution rate for release of tablet content
- Uniformity of weight/ contents of tablets and sachets
- Content of active pharmaceutical ingredient (s) – Assay

## Methodology contd.



- Amodiaquine - assay

The quantity of Amodiaquine in milligrams of Amodiaquine dihydrochloride dihydrate(USP) by the formula

$$\frac{21.68C (Au/As) \times 0.7655}{\text{Amount of Amodiaquine weighed}}$$

**C** – Concentration in µg/ml of the Amodiaquine HCl RS

**Au** – Absorbance of the test solution

**As** – Absorbance of the standard solution

**0.7655** – Conversion factor of Amodiaquine base for the Amodiaquine dihydrochloride dihydrate salt

## Methodology contd.



### Amodiaquine - Dissolution

- The dissolution parameters for Amodiaquine tablets (USP) were as follows.

Apparatus	:	Apparatus 2 (paddle)(USP)
Stir rate	:	50 rpm
Bath temp	:	37 °C + 0.5 °C
Medium	:	Water 900ml
Q value	:	75%
Time	:	30 minutes

***Amount of Amodiaquine dissolved after 30minutes expressed as % of labelled claim***

## Methodology contd.



### • Artesunate assay

- The content of Artesunate was determined by HPLC (IP Vol 5)
- HPLC parameters
  - HPLC Column : Princetonspher C18, 5µ, 250mm x 46mm
  - Mobile phase : Acetonitrile : Phosphate Buffer pH 3.0  
50 : 50
  - Detection : UV @ 216nm
  - Flow rate : 2.0ml/min
  - Injection volume : 20µL

## Methodology contd.



### Artesunate - Dissolution

- The dissolution parameters for Artesunate tablets (IP) were:

Apparatus	:	Apparatus 2 (paddle) of the USP
Stir rate	:	75 rpm
Bath temp	:	37 °C ± 0.5 °C
Medium	:	Water 900ml
Q value	:	60 %
Time	:	30 minutes

## Methodology contd.



### • DihydroArtemisinin assay

- The content of dihydroartemisinin was determined by HPLC (IP Vol 5)

- HPLC parameters:

HPLC Column	:	Princeton spher C18, 5µ, 250mm x 46mm
Mobile phase	:	Acetonitrile : Water 50 : 50
Detection	:	UV @ 216nm
Flowrate	:	1.0ml/min
Injection volume	:	20µL

## Methodology contd.



### Dihydroartemisinin - Dissolution

- The dissolution parameters for Artesunate tablets (IP) were:

Apparatus	:	Apparatus 2 (paddle) (USP)
Stir rate	:	75 rpm
Bath temp	:	37 °C $\pm$ 0.5 °C
Medium	:	Water 900ml
Q value	:	60%
Time	:	30 minutes

## Methodology contd.



### Analysis for Artesunate/Amodiaquine Fixed Dose Combination

- The content of Artesunate and Amodiaquine in these preparations were analysed as per the respective monographs in of Artesunate and Amodiaquine (IP & USP)

## Methodology contd.



### **Artesunate/Amodiaquine Fixed Dose Combination - Dissolution**

- The dissolution rate of both the Artesunate and Amodiaquine were determined separately as per the methods described above for Artesunate and Amodiaquine.

## Results



### **Physical appearance**

#### **88%-Artemisinin derivatives**

#### **95%-Amodiaquine**

Defects observed includes:

- Brownish pinkish discolouration (Artesunate)
- Brown spots on tablets (Amodiaquine)
- Empty blister tablet hole

#### **Discolouration may be a sign of:**

- Degradation of API

## Results contd.



### Identification (100%)

- Positive for all samples

### Assay (100 %)

- All samples analysed passed assay

## Results contd.



### Dissolution

- **Amodiaquine**

Met the USP	:	17	(47 %)
Did not meet USP	:	19	(53 %).

- Artemisinin derivatives (Artesunate and Dihydroartemisinin),

Met the USP	:	28	(78 %)
Did not meet USP	:	8	(22 %).

## Results contd.



- Total compliance to parameters considered
- **For Artemisinin derivatives**
  - 36 (88%) passed physical appearance
  - 41 (100%) passed identification
  - 41 (100%) passed assay
  - 28 (78%) passed dissolution

## Results contd



- **For Amodiaquine**
  - 39 (95%) passed physical appearance
  - 41 (100%) passed identification
  - 41 (100%) passed assay
  - 17 (47%) passed dissolution

## Discussion



- Dissolution failure rate high with Amodiaquine tablets.
- Also same batch no. from different locations gave different dissolution profile

May be due to:

- poor formulation
- stability problems
- Critical processes not validated

## Discussion contd.



- Discolouration of Artemisinin derivatives & brown spots on Amodiaquine is a sign of degradation and needs to be investigated further. May be due to
  - impurities
  - related substances
- Empty blister tablet hole may be due to poor supervision of packing line

### **Next steps**



- 4 different batches shall be analysed to establish findings
- Physical appearance of discoloured tablets to be investigated
  - Comparism with retained samples
  - Impurities and related substances to be tested for
- Training in process validation

### **Next steps contd.**



- Industry to perform process validation
- Training in stability studies
- Industry to perform stability studies
- Constantly monitor the quality of ACT/Amodiaquine combinations on the market

## **Conclusion**



- Assay, identification and physical appearance satisfactory
- More work need to be done on dissolution
- Need to do a baseline study to agree on acceptable dissoluton standards.
- Industry is to be fully integrated into the process

The Chemistry of Artesunate, Amodiaquine, Sulfadoxine, and Pyrimethamine,  
Mr. Eric K. Boateng, FDB

# CHEMISTRY OF ARTEMISININ GROUP OF DRUGS, AMODIAQUINE AND SULPHADOXINE/ PYRIMETHAMINE

**PRESENTED BY  
ERIC KARIKARI-BOATENG**

**FOOD AND DRUGS BOARD LABORATORY.**

## INTRODUCTION:

The qinghaosu (artemisinin) group of drugs was first isolated by Chinese scientists from the plant *Artemisia annua* in 1972. The parent compound is artemisinin. The following underlisted derivatives are now available and used widely in the treatment of malaria.

1. Dihydroartemisin
2. Artesunate
3. Artemether
4. Arteether

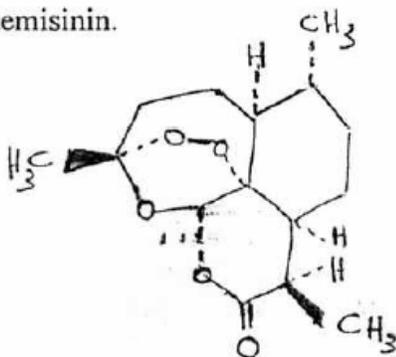
## CHEMISTRY

Artemisinin (parent compound)

**CHEMICAL NAME:** [3R - (3 $\alpha$ , 5 $\alpha$ , 6 $\beta$ , 8 $\alpha$ , 9 $\alpha$ , 12 $\beta$ , 12aR\*)]  
- Octahydro-3,6,9 - trimethyl - 3, - 12 epoxy  
- 12H - pyranol [3,4 - j] - 1,2 - benzodioxepin  
- 10 (3H) - one.

**APPROVED NAME** - Artemisinin.

STRUCTURE



**CHEMICAL NAME**

- (3R, 5aS, 6R, 8aS, 9R, 12S, 12aR) - Octahydro- 3, 6, 9, trimethyl 3, 12, epoxy-12 H-  
pyrano [4, 3, - j] -1, 2 - benzodioxepin - 10 (3N) - One

**APPROVED NAME:** (INN) - Artemisinin.

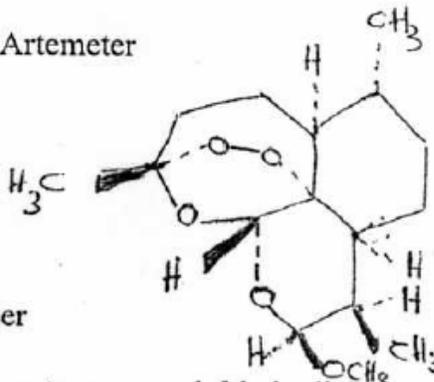
**PHYSICAL PROPERTIES.**

- Fine white crystalline powder.
- Very slightly soluble in water, very soluble in CH<sub>2</sub>CL<sub>2</sub>, freely soluble in ethanol (-750g/L) and Acetone.
- Melting range 132 – 135<sup>0</sup>C

**CHEMICAL NAME:**

(3R, 5As, 6R, 8As, 9R, 10S, 12R, 12Ar) – Decahydro – 10 – methoxy – 3, 6, 9, trimethyl – epoxy – 12N – pyrano [4, 3, -1, 2 benzodioxepin].

**APPROVED NAME:** Artemeter



**PHYSICAL PROPERTIES**

- White crystalline powder
- Practically insoluble in water, very soluble in dichloromethane, and acetone, freely soluble in ethyl acetate and dehydrated alcohol.
- Melting point 86.0 – 90.0<sup>0</sup>C

**CHEMICAL NAME:**

[3R – (3&, 5a β, 9&, 10&, 12 β – 12aR\*)] – 10 – Ethoxydecahydro – 3, 6, 9, trimethy 1 – 3, 12 – epoxy – 12H – pyrano [4, 3, j] – 1, 2, benzodioxepin.

**APPROVED NAME:** (INN): Arteether, Dihydroartemisinin ethylether.

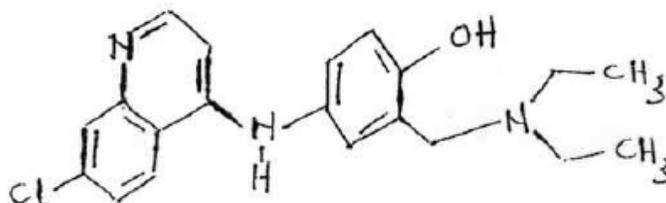
**PHYSICAL PROPERTIES**

- White crystalline solid
- Melting point 80 – 82<sup>0</sup>C
- Practically insoluble in water, very soluble in CH<sub>2</sub>CL<sub>2</sub> and acetone.

**CHEMICAL NAME:** Phenol, 4, - [C7 – chloro-4-quinolinyl) amino] – 2 - [diethylamino) - methyl]

**APPROVED NAME: AMODIAQUINE.**

Commonly used salt. Amodiaquine Hydrochloride C<sub>20</sub>H<sub>22</sub>ClN<sub>3</sub>O.2HCL.2H<sub>2</sub>O

**STRUCTURE****PHYSICAL PROPERTIES. AMODIAQUINE**

- Yellow bitter crystals
- Melting point 150 – 160<sup>0</sup>C
- Soluble water, sparingly soluble in alcohol and slightly soluble in benzene, chloroform and ether.

**AMODIAQUINE HYDROCHLORIDE**

- Yellow crystalline powder
- Melting point 243 – 244<sup>0</sup>C
- Soluble in water and alcohol.

**CHEMICAL NAME:** 4 – amino-N-(5, 6 – dimethoxy – 4 – pyrimidinyl) – N – (5, 6 – Dimethoxy – 4 – pyrimidinyl) sulfanilamide.

**PHYSICAL PROPERTIES.**

- Needless white to off white crystalline powder
- Melting point 156 – 157<sup>0</sup>C
- (C = 1.64 in chloroform)
- Soluble in most aprotic solvents
- Slightly soluble in oil.

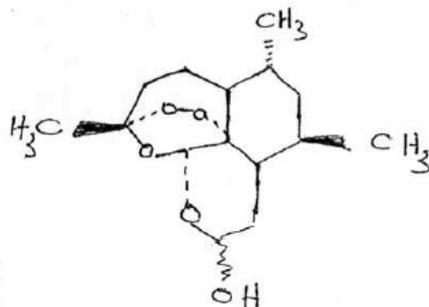
**CHEMICAL NAME:**

Dihydro derivative of artemisinin

**APPROVED NAME:**

(INN) – Dihydroartemisinin

- Main metabolite of Artemisinin, Artesunate,  $\beta$  Artemether and Arteether.

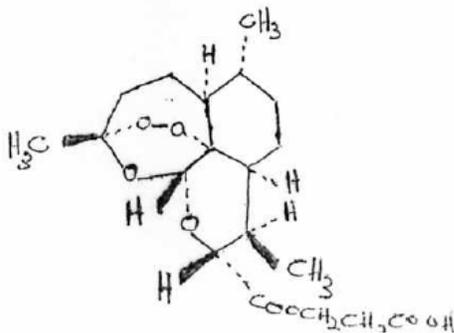


Dihydroartemisinin  
Physical Properties

- White to off white crystals
- Melting point 164 – 165<sup>0</sup>C
- Slightly soluble in water. Soluble in CH<sub>2</sub>CL<sub>2</sub>.

CHEMICAL NAME - [3R – (3&, 5&  $\beta$ , 6  $\beta$ , 8a  $\beta$ , 9&, 10 $\beta$ , 12  $\beta$ , - 12aR\*) – Butanedioic acid mono (decahydro -3, 6, 9 trimethyl) -3, 12 epoxy-12H-pyrano [4,3-j ] 1, 2 benzodioxepin – 10 – y1) ester.

**APPROVED NAME** – Artesunate (Artesunic acid)

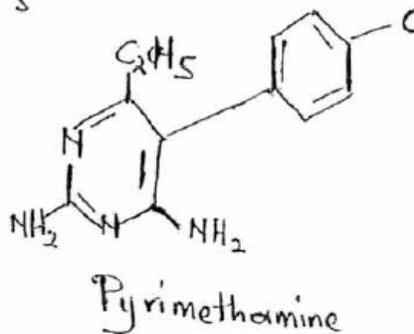
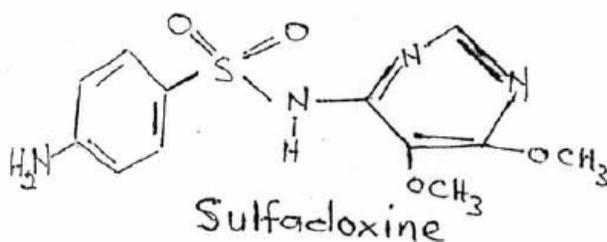


**APPROVED NAME:** (INN) – SULFADOXINE.

**CHEMICAL NAME:** 5 – (4 – Chlorophenyl) – 6 ethylpyrimidine – 2,4 – diamine.

**APPROVED NAME (INN) – PYRIMETHAMINE**

STRUCTURES



**PHYSICAL PROPERTIES: SULFADOXINE**

- White or yellowish – white crystalline powder or crystals.
- Melting point – 198<sup>0</sup>C with decomposition.
- Slightly soluble in alcohol and in methanol
- Practically insoluble in ether
- It dissolves in solutions of alkali hydroxides and in dilute mineral acids.

**PYRIMETHAMINE**

- An almost white, crystalline powder or colourless crystals.
- Melting point 239 – 243<sup>0</sup>C
- Practically insoluble in water, slightly soluble in alcohol, very slightly soluble in ether.

**Formulation Practices for ACT Dosage Forms, Mr. J. Y. Binka, FDB**

**FOOD AND DRUGS BOARD  
PROGRAMME**

GOOD FORMULATION PRACTICES TRAINING ON  
ACTS FOR LOCAL INDUSTRY

**AT**  
KAMA CONFERENCE CENTRE, ACCRA, 12<sup>TH</sup>  
AUGUST 2005

**TOPIC**  
FORMULATION PRACTICES OF ACT DOSAGE  
FORMS

**BY: JAMES Y. BINKA**  
**PHARMACEUTICAL CONSULTANT**

**ARTEMISININ-BASED  
COMBINATION THERAPY**

1.0 ARTESUNATE PLUS  
SULFADOXINE/PYRIMETHAMINE

2.0 ARTESUNATE PLUS AMODIAQUINE

3.0 ARTEMETHER/LUMEFANTRINE

COMBINATION DRUGS IN DEVELOPMENT:  
CHLORPROGUANIL – DAPSONE –  
ARTESUNATE

PYRONARIDINE – ARTEMISININ DERIVATIVE

PIPERAQUINE – DIHYDROARTEMISININ

REFERENCES:

1. COMBINATION THERAPY IN MALARIA –  
ORIENTATIONS AND OPTIONS FOR THE  
AFRICAN REGION, WHO BRAZAVILLE, 2004

2. THE QUALITY OF ANT-MALARIALS – A  
STUDY IN SELECTED AFRICAN COUNTRIES –  
WHO, GENEVA, 2003

## PRE-FORMULATION CONSIDERATION (1)

■ PHYSICOCHEMICAL PROPERTIES OF THE ACTIVE INGREDIENTS

- CHEMICAL STRUCTURE
- SPECTROSCOPY
- SOLUBILITY

- \*AQUEOUS
- \*pKa
- \*SALT S
- \*SOLVENTS
- \*PARTITION COEFFICIENT – K
- \*DISSOLUTION
- \*MELTING POINT

## **PRE-FORMULATION CONSIDERATION (2)**

- ASSAY DEVELOPMENT
- STABILITY (IN SOLUTION AND SOLID STATE)
- MICROSCOPY
- POWDER FLOW
  - BULK DENSITY
  - ANGLE OF POWDER
- EXCIPIENT COMPATIBILITY

## **FACTORS ALTERING PERFORMANCE OF DRUGS**

PARTICLE SIZE – CHLORAMPHENICOL  
GRISEOFULVIN

CO-SOLUTE AND COMPLEX FORMATION

SALTING IN

CLATHRATE FORMATION – e.g., SULFATHIAZOLE

## **FACTORS ALTERING PERFORMANCE OF DRUGS (2)**

SOLID-IN-SOLID SOLUTION COMPLEX – e.g., drugs dissolved in a melt of mannitol or other carbohydrate

CHEMICAL VARIATION – CHANGES FORMATION OF SALTS

AMORPHOUS AND CRYSTALLINE

IN GENERIC

AMORPHOUS NOVOBIOCIN, CHLORAMPHENICOL ESTERS – MORE ACTIVE CRYSTALLINE FORM

## **FACTORS ALTERING PERFORMANCE OF DRUGS (3)**

- ANHYDROUS FORM, HYDRATES, AND SOLVATE, e.g., AMPICILLIN, CAFFEINE
- ABSORPTION – e.g., ANTACIDS – MAGNESIUM, ALUMINIUM
- MANUFACTURING FACTORS
- INCREASING AMOUNTS BINDERS-IN GRANULES-HARDNESS
- INCREASING AMOUNTS OF LUBRICANTS

## **FACTORS ALTERING PERFORMANCE OF DRUGS (4)**

- DECREASES HYDROPHILICITY
- COMPRESSION OF HARD GRANULE (75)

Use of Starch and Other Binding & Disintegrating Agents in Tablet Formulation,  
Dr. S. N. B. Gaizer, DanAdams Pharmaceuticals

**THE USE OF STARCH AND OTHER  
BINDING/DISINTEGRATION AGENTS  
IN TABLET FORMULATIONS**

**FDB INDUSTRIAL TRAINING.  
BY DR. SAM NII-BORTIER GAIZER  
PhD (FWAPCP) (MP5G)  
AUGUST 12<sup>TH</sup> 2005  
VENUE: KAMA CONFERENCE CENTRE**

STARCH & OTHER DISINTEGRANTS IN (ACT)  
FORMULATIONS

- **PRINCIPLES IN FORMULATION:**
  - STARCH CHEMICAL PROPERTIES AND ORIGIN.
  - PHYSICAL PROPERTIES
  - COMMON USES: FOOD AND ALLIEDS
- **PHARMACEUTICAL USES:**
  - PHARMACEUTICAL FORMULATIONS WITH PURE STARCH.
- **VARIOUS TYPES OF STARCHES IN FORMULATIONS:**
  - (1) PRE-GELATINIZED STARCH
  - (2) SODIUM STARCH GLYCOLATE
  - (3) STARCH ACETATE

## **OTHER DISINTEGRANTS**

- 1. POVIDONE (KOLIDONE/PVP)**
- 2. CARBOXYMETHYLE CELLULOSE (CMC)**
- 3. MICROCRYSTALLINE CELLULOSE (MCC)  
AVIGEL**
- 4. HYDROXYPROPYL CELLULOSE**
- 5. CARMELLOSE**
- 6. COLLOIDAL SILICON DIOXIDE (AEROSIL)**
- 7. CROSS-POVIDONE**

## **WHAT IS A FORMULATION?**

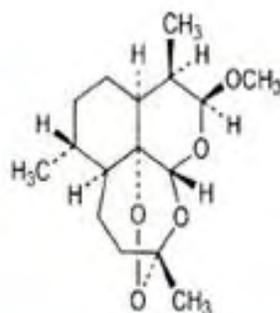
FORMULATION IS THE BRANCH IN PHARMACEUTICAL TECHNOLOGY THAT DEALS WITH THE SCIENCE OF DOSAGE-FORM DESIGN.

### **THE THREE MAJOR CONSIDERATIONS IN THE DESIGN OF DOSAGE FORMS:**

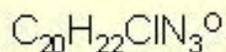
**The physicochemical properties of the drug itself:  
active ingredient and excipients—e.g., artemisinin-  
based combinations (ACT): artesunate + amodiaquine  
hydrochloride in Ghana**

## STRUCTURE OF ARTESUNATE

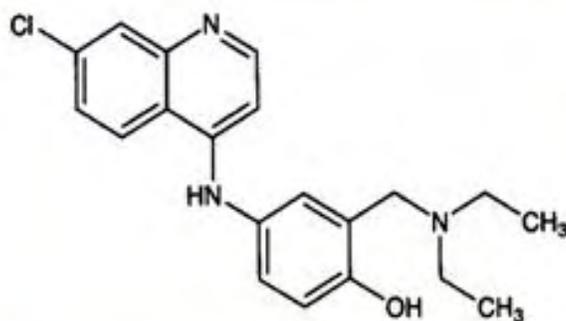
- *Monographs for antimalarial drugs*
- 187
- *Artemetherum*
- *Artemether*
- C<sub>16</sub>H<sub>26</sub>O<sub>5</sub>
- Relative molecular mass: 298.4
- Chemical name:  
(3*R*,5*a**S*,6*R*,8*a**S*,9*R*,10*S*,12*R*,12*a**R*)-Decahydro-10-methoxy-3,6,9-trimethyl-3,12-epoxy-12*H*-pyrano[4,3-*j*]1,2-benzodioxepin;  
CAS Reg.
- No. 71963-77-4.
- Description. White crystals or a white crystalline powder
- Solubility. Practically insoluble in water; very soluble in dichloromethane
- R and acetone R; freely soluble in ethyl acetate R and dehydrated ethanol
- R.



## AMODIAQUINE STRUCTURE



[(7-chloro-4-quinolyl)amino]-2-(diethylamino)-methylphenol



THE THREE MAJOR CONSIDERATIONS IN  
THE DESIGN OF DOSAGE FORMS  
(continued)

- 2. (a)** Biopharmaceutical considerations, such as how the route of administration of the dosage form affects the rate and extent of drug absorption into the body.

**Bioavailability (1)**

To achieve or improve bioavailability, it is important to know the following sequence of events—

How the Drug in a Tablet Becomes Bioavailable

Ingestion

Disintegration of the particles  
in the gastrointestinal tract

Distribution of the particles  
in the gastrointestinal tract

Dissolution of the drug in the  
gastric or intestinal juice

Absorption of the drug by the  
mucous membrane of the stomach or intestine

## **Bioavailability (2)**

- The disintegration of the tablet or capsule can be regarded as the first step on the path to bioavailability and to the pharmacological action of the drug. To achieve this, it is usually necessary to add a disintegrant.
- Different disintegrants work in different ways, which can involve swelling, wicking and deformation effects, and the repulsion of charged particles.

## **THE THREE MAJOR CONSIDERATIONS IN THE DESIGN OF DOSAGE FORMS (continued)**

2. (b) Biopharmaceutical considerations, such as disintegration, dissolution, absorption, bioavailability, stability, microbiological aspects, incompatibility

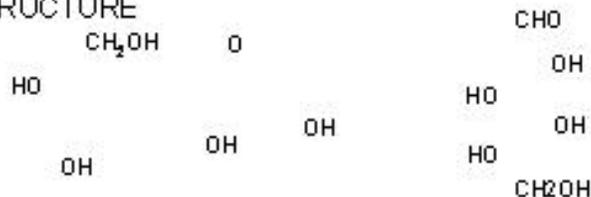
THE THREE MAJOR CONSIDERATIONS IN THE DESIGN OF DOSAGE FORMS (continued)

Therapeutic considerations of the disease state to be treated, which in turn determine the most suitable type of dosage form, possible routes of administration, and the most suitable duration of action and dose frequency for the drug in question, e.g.—injections, tablets and syrups, topical preparations, ointments, creams, lotions, suspensions, suppositories, transdermals, sprays, sublingual dosage forms

**ORIGIN**

1. Photosynthesis—green matter  $\text{CO}_2$  starch  
sucrose-glucose + fructose

2. STRUCTURE



GLUCOSE:  $\alpha$ -D-glucose

Cyclohexane—one divalent oxygen in the ring

(OH). Many hydroxyl groups-(alcohol groups).

Sweetening and solubility - $\alpha$ -D glycosides.

Five asymmetrical carbons—(optical isomers).

## CHEMICAL PROPERTIES OF STARCH

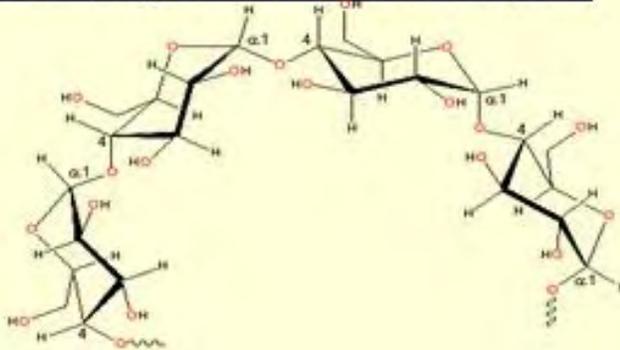
- Starch consists of two types of molecules, amylose (normally 20–30%) and amylopectin (normally 70–80%). Both consist of polymers of  $\alpha$ -D-glucose units in the  $4C_1$  conformation. In amylose, these are linked  $-(1\rightarrow4)-$ , with the ring oxygen atoms, all on the same side, whereas in amylopectin about one residue in every twenty or so is also linked  $-(1\rightarrow6)-$  forming branch-points. The relative proportions of amylose to amylopectin and  $-(1\rightarrow6)-$  branch points both depend on the source of the starch, e.g., amylo maize contains over 50% amylose, whereas "waxy" maize has almost none (~3%) [260].

IDENTIFICATION: suspend in water and boil  
Mucilage – Fehlings reagent – iodine sol. R.L- BlueBlack

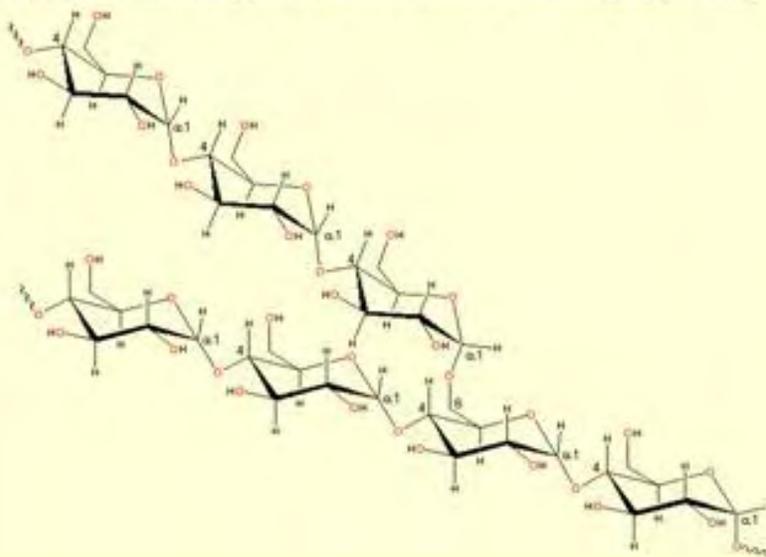
## STARCH

- Chemical composition: INN  $C_{12}(H_2O)_{11}$**   
**B.P. SPECIFICATION:**

### **Representative partial structure of amylose**



**Representative partial structure of amylopectin**



**PHYSICAL PROPERTIES OF STARCH**

- Of the two components of starch, amylose has the most useful functions as a hydrocolloid. Its extended conformation causes the high viscosity of water-soluble starch and varies relatively little with temperature. The extended loosely helical chains possess a relatively hydrophobic inner surface that is not able to hold water well and more hydrophobic molecules such as lipids and aroma compounds can easily replace this. Amylose forms useful gels and films. Its association and crystallization (retrogradation) on cooling and storage decreases storage stability causing shrinkage and the release of water (syneresis). Increasing amylose concentration decreases gel stickiness but increases gel firmness. Amylopectin interferes with the interaction between amylose chains (and retrogradation) and its solution can lead to an initial loss in viscosity and followed by a more slimy consistency.

Microbiological grade  $<10^3$  glucose/fructose  
Amylopectin/maltodextrin

## COMMON USES

- Starch as a form of carbohydrate is a source of food for energy but used in other areas for other purposes.
- E.g., all natural creams, antiperspirants, cationic cleansing products, cationic lotions and creams, color cosmetics, concealer, conditioners, creme rinses, creams, emulsions, eye liner, facial cleansers, facial creams, gels, high salt-containing gels, leave-in conditioners, liquid make-up, liquid soaps, liquid talc, low-surfactant or surfactant-free emulsions, make-up, ointments, personal wash products, protective creams, shampoos, shave creams, skin lotions and creams, sunscreens, water-resistant sunscreens

## PHARMACEUTICAL APPLICATIONS

### USED IN

**Suspensions: Viscosity /adhesive**

**Lotions**

**Creams**

### Pharmaceutical Uses

#### TABLETING

**(1) Binder (wet & dry granulations)**

**(2) Disintegrant**

**(3) Lubricant**

**(4) (Filler) diluent**

**(5) Slow release (retard)**

**(6) Anti-tacking agent (sugar/starch)**

**(7) Placebo**

**(8) Film coating**

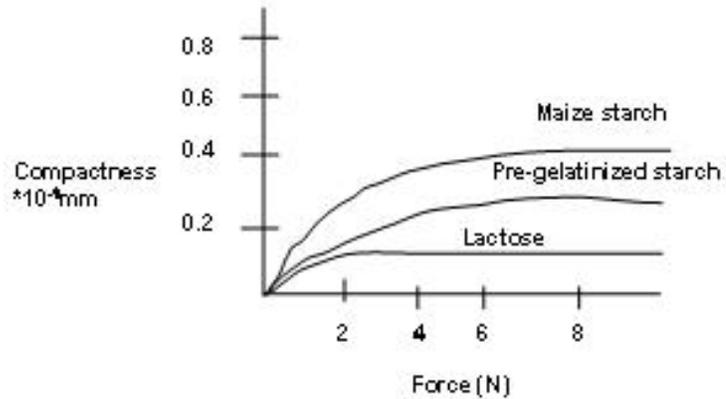
## STARCH APPLICATION IN PHARMACEUTICAL FORMULATION (ACT)

Technology	<b><u>TABLETING</u></b>	
	<u>Excipient</u>	<u>Rheology</u> Compressibility Tablet wt.
1. Filler	10–70%	
2. Disintegrant	5–20%	
3. Glidant	1–10%	
4. Lubricant	1–10%	
5. Binding agent	1–15%	
Internal core	10–60%	
External core	1–20%	

## STARCH DERIVATIVES IN ACT FORMULATIONS

- MAIZE STARCH
- PRE-GELATINIZED STARCH
- SODIUM STARCH GLYCOLATE
- STARCH ACETATE (Corex)
- CARBOXYMETHYL STARCH SODIUM

## STARCH COMPRESSIBILITY



## PRE-GELATINIZED STARCH

Mechanically processed starch to obtain better physical qualities—

1. Compressibility
2. Binder – as binder solution of  
4–8% are ideal  
4–12%

## SODIUM STARCH GLYCOLATE

Starch disintegrants: Explotab  
(extragranular and intragranular)—

1–20% application as a disintegrant in  
artesanate combination therapy  
formulations

## STARCH ACETATE

- Starch acetates can be used as direct compression, matrix forming material. This novel technology concept enables a flexible formulation design. The specific drug release profiles can be achieved simply by mixing high substitution degree starch acetate (ds.2.9) with low substitution degree starch acetate (for example, 0.05) or with inert pharmaceutical excipients (microcrystalline cellulose, lactose). The technology allows the controlled release matrix tablet development and production with minimized number of excipients and process steps.

## OTHER DISINTEGRANTS

1. POVIDONE (KOLIDONE/PVP)
2. CARBOXYMETHYLE CELLULOSE (CMC)
3. MICROCRYSTALLINE CELLULOSE (MCC) AVICEL
4. HYDROXYPROPYL CELLULOSE
5. CARMELLOSE
6. COLLOIDAL SILICON DIOXIDE (AEROSIL)
7. CROSS-POVIDONE

## IMPORTANCE OF BINDING AGENTS/DISINTEGRANTS

- Acceleration of tablet disintegration and therefore also of dissolution and bioavailability of the active substances as a result of predictable swelling (disintegration effect).
- Improvement of dissolution and bioavailability of drugs by complex formation.
  - Selective adsorption by complex formation
  - Stabilization as a hydrophilic polymer
  - Adsorption of water
  - Taste-masking effect

## SAMPLE TABLET FORMULATION

### ARTESUNATE TABLET

Artesunate	200mg	BP	Active ingredient
Maize starch	64mg	BP	Diluent
Microcrystalline cellulose	32mg	BP	Dispersing agent & lubricant
Povidone	16mg	BP	Binder
Sodium starch Glycolate	20mg	BP	Disintegrant
Colloidal silicon dioxide	6mg	BP	Aggregant & lubricant
Magnesium stearate	4mg	BP	Lubricant

**NOTE:** Both dry and wet granulation can be used with varied pharmaceutical technology (e.g., intermediate wet granulation for direct compression)

### WHY THE CHOICE OF DISINTEGRANTS AND BINDING AGENTS ARE IMPORTANT

1. Incompatibility of excipients and active ingredients
2. Binding agents should be of good drying time
3. Solvent for binding agents should be of good volatile range (e.g., ethyl alcohol)
4. Binders/disintegrants should have good adsorptive properties to preserve active ingredients from high relative humidity effect
5. Very stable binders/disintegrants should be employed
6. Choice of binders/disintegrants should made for intended design
7. Product quality is not only determined by active ingredients presence but its designed biopharmaceutical properties, etc.
8. All artesunate products should be film-coated to ensure product stability for all ACT products

## **GOOD BREAKFAST (ATP) Release**

### TRY AND TASTE

Corn starch	5g
Water	20g
Sugar	3g
Salt	0.1g



**THANK YOU!!!**

**Specifications for the Production of ACTs, Mr. E. Y. Kwarteng, FDB**



## **OBJECTIVES**



- **Ensure a rapid, long-lasting clinical cure for individual patients with malaria**
- **Prevent progression of uncomplicated malaria to severe disease and death**
- **Shorten clinical episodes of malaria and reduce the occurrence of malaria-associated anaemia in populations residing in areas of high malaria transmission**
- **Delay the development and spread of resistance**

## **SPECIFICATIONS AND DOCUMENTATION REQUIREMENTS**



- **Development pharmaceuticals**
- **Analytical methods and validation**
- **Bioavailability, bioequivalence and clinical trials**

## **DEVELOPMENT PHARMACEUTICS (1)**



- **ACT formulations should contain the necessary internationally approved excipients to enhance product bioavailability.**
- **All products must have evidence of having been taken through accelerated stability studies, conducted at the WHO/ICH zone IV classification.**
- **Set factory specifications for active pharmaceutical ingredients and excipients as part of comprehensive GMP and GFP applications.**

## **DEVELOPMENT PHARMACEUTICS (2)**



- **Product registration requires these as well as product master file, and a report of product development and validation protocol.**
- **Dosage for children should be spelled out and differentiated from dosage for adults.**
- **Co-blister packing of individual artesunate and amodiaquine is preferred. For single fixed-dose combination, FDB criteria for fixed-dose combination would be applied.**

## **ANALYTICAL METHODS AND VALIDATION (1)**

- **For co-blister formulations the product should be analysed as per the monographs of artesunate and amodiaquine in the International Compendia recognised by the Food and Drugs Law (i.e., schedule I)**
- **United States Pharmacopoeia (USP)**
- **British Pharmacopoeia (BP)**
- **European Pharmacopoeia (Eur. P)**

## **ANALYTICAL METHODS AND VALIDATION (2)**

- **Chinese Pharmacopoeia (CP for artesunate)**
- **International Pharmacopoeia (IP)**
- **In vitro dissolution as per these monographs would have to be conducted to establish the bioequivalence status to the products.**

## **ANALYTICAL METHODS AND VALIDATION (3)**



- **For the fixed-dose combination, the following are recommended:**
  - **Drug master file**
  - **Process validation for manufacturing activities including validation protocol and report.**
  - **Monograph for the fixed-dose combination**
  - **Analytical method validation for the final product analysis**
  - **Accelerated stability data**

## **BIOAVAILABILITY, BIOEQUIVALENCE, AND CLINICAL TRIALS (1)**



- **For co-blisters preparations, the manufacturer will conduct bioequivalence studies with the innovator drugs or lead market brand.**
- **For the fixed-dose combination the following requirements are to be met:**
  - **Bioequivalence studies with the innovator/ lead market brands of artesunate and amodiaquine**
  - **Validated bioanalytical methods used in bioequivalence studies**
  - **Phase III clinical trials showing product efficacy should be conducted**

## **BIOAVAILABILITY, BIOEQUIVALENCE, AND CLINICAL TRIALS (2)**



- **Artesunate and amodiaquine in the formulation should not be less than 75% in 30 minutes in the in vitro dissolution test.**
- **Stability studies conducted in accordance with WHO guidelines in climatic zone IV.**

## **SPECIFICATIONS FOR PRODUCTION (1)**



- **The following specifications have been recommended for the registration of the anti-malarial combination:**
  - **The generic artesunate/amodiaquine should be used by all companies.**
  - **Should any branding be made, the font size of the brand name should be half of the generic name and should be written below.**
  - **The new combination should be tablets in blister packs with rigid lines to clearly differentiate the recommended daily doses.**

## SPECIFICATIONS FOR PRODUCTION (2)

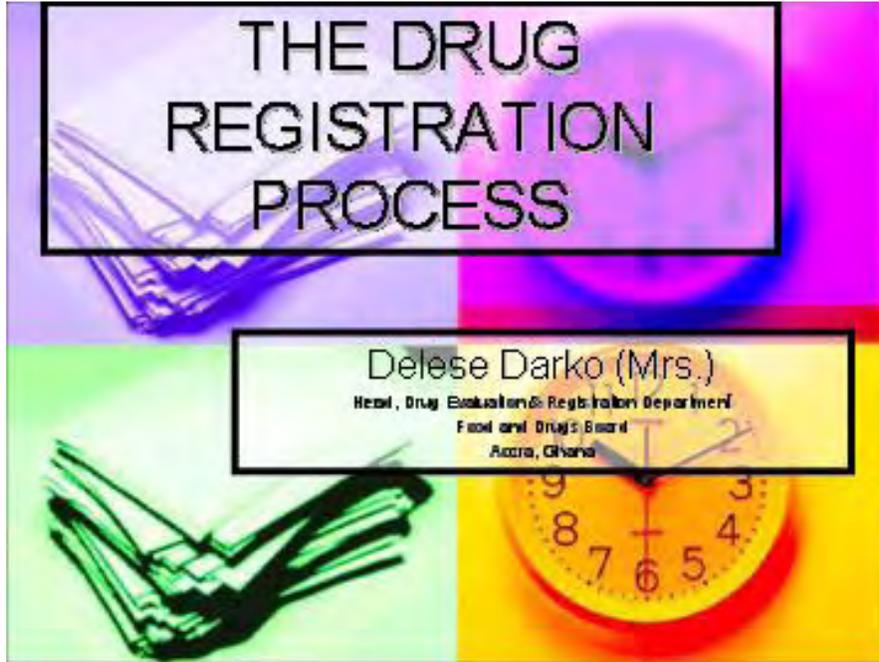
- For adults the amodiaquine may be two tablets of 300mg strength each.
- For all the other age groups only one amodiaquine tablet of the required strength shall be permitted together with a single tablet of artesunate.
- The natural colours of artesunate and amodiaquine must be maintained.
- The following tablet descriptions and colour codes for aluminium foils are recommended for adoption.

## Description and Colour Coding

AGE (YEARS)	DO SAGE		DO SAGE FORM	COLOUR CODE
Adult 14 and above	Artesunate 200mg	Amodiaquine 600mg as kita	Tablets, capsule, may be film coated, elongated, or elliptical in shape	Red
7-13	Artesunate 100mg	Amodiaquine 300mg as kita	Tablets, capsule, round shape, and may be film coated	Blue
1-6	Artesunate 50mg	Amodiaquine 150mg as kita	Dispersible tablets, round shape	Pink
Infants below 1	Artesunate 25mg	Amodiaquine 75mg as kita	Dispersible tablets, round shape	Orange



**Requirements for Medicine Registration, Mrs. Deles Darko, FDB**





## Legislation

Food and Drugs Law, 1992 P.N.D.C.L. 305B, as amended by Act 523, 1996.

- Section 18 – "No person shall manufacture prepare, sell.... any drug etc unless the article has been registered with the Food and Drugs Board."
- Section 25 – "The Board shall keep separate registers for the registration of all products regulated..."
- Section 26 – Penalties



## Guidelines and Application Forms

- Guidelines and application forms exist for:
  - Registration
  - Renewal of registration
  - Variation of a registered medicine
- Guidelines exist for:
  - Conducting stability studies
  - Conducting bioequivalence studies
- Sample schedule
  - Guide to quantity of samples to submit
- Fee schedule
  - Lists the application fees to be paid



## Submission of Application

- Covering letter requesting registration
- Samples of medicine
- Dossier
  - Completed application form with signed declaration
  - Certificates of analysis
  - Certificate of Pharmaceutical Product
  - Batch records, etc.
- Application fee



## Evaluation Process

- Preliminary evaluation of medicine
  - Labelling (brand/generic name, batch no., manuf. & exp. date, specific dosage, net volume, manufacturing premises address, etc.)
  - Review of package inserts
  - Suitability/effectiveness of closures
  - Inclusion of appropriate plastic dosing measures
  - Quality/integrity of both primary & secondary package
- Acknowledge receipt – 7 days



## Evaluation

- Details of medicine and manufacturing and distributor captured in SIAMED software programme
  - Name (brand & generic)
  - Name of manufacturer, local agent
  - Quantity and specification of active ingredient(s)
  - Quantity of excipient(s)
  - Source of raw materials



## Dossier Evaluation

Dossier evaluated in accordance with guidelines:

- Review of product and company details, and declaration.
- Review of general product specifications
- Review of particulars of manufacturing procedure and related controls
  - Source and certificates of analysis for all ingredients
  - Drug master file and process validation protocols
  - Batch records
  - Stability study data



## Dossier Evaluation (2)

- Review of administrative status of medicine
  - Registration in other countries
  - Certificate of Pharmaceutical Product (CPP)
- Review of toxicological, pharmacological, and clinical data
- Comprehensive review of package insert and label



## Evaluation Strategy

- Desktop research on each medicine
- Internal evaluators used
- Expert opinion/advice may be sought
- Dossier evaluation retreat strategy adopted



### Laboratory Analysis

Medicines are analyzed according to specifications by which they are manufactured, e.g., BP, PhEur, USP

- Physicochemical analysis – pH, resuspendability, disintegration, dissolution, assay, etc.
- Microbiological analysis - aerobic plate count, yeast, mould.
- In addition: anaerobic count is done for suspensions which contain bentonite as suspending agent.



### Premises Inspection

#### Inspectorate department:

- Assesses manufacturer's compliance to current codes of Good Manufacturing Practice (GMP)
- Ascertains capacity of existing facility to add new product



### Registration Meeting

Collation of results:

- Dossier
- Laboratory
- GMP inspection
- ◆ Tabular presentation of recommendations
- ◆ Review by drug committee
- ◆ Process takes about 2–3 months



### Communicate Registration Outcome

- Approved
  - Registration number issued
  - Certificate printed
- Deferred
  - Supplementary documentation requested
- Rejected/not recommended
  - Unjustifiable/irrational combination
  - Fails laboratory analysis



### Registration Confirmed

- Product registers updated
- SIAMED processing steps completed
- Registration validity – three (3) years

Process takes about 3–4months



# THANK U!!

**Dissolution Testing, Mr. Eric K. Boateng, FDB**

**DISSOLUTION TESTING OF  
SOLID DOSAGE FORMS:  
IMMEDIATE AND MODIFIED  
PREPARATIONS**

**ERIC KARIKARI-BOATENG  
FOOD AND DRUGS BOARD  
LABORATORY, GHANA  
AUGUST 2005**

**DEFINITION**

- ◆ Dissolution (test) is the process by which a solid substance enters into a solvent (dispersion medium) to yield a solution. It is simply a process by which a solid substance dissolves and can be measured by a change in solute concentration. Dissolution is controlled by the affinity between the solid substance and the solvent (medium).

## **SIGNIFICANCE OF DISSOLUTION TESTING**

- ◆ Can be an indicator of in vivo performance.
- ◆ Serves as a quality control test by providing evidence of the product's physical consistency and manufacturing process.
- ◆ Serves as a quality assurance tool.
- ◆ Is extremely useful for product stability.
- ◆ Useful in development pharmaceuticals (early stage of product and formulation development).
- ◆ Is a critical regulatory and compendial requirement in the testing of oral solid dosage forms.
- ◆ Enables regulatory agencies to make approval decisions pertaining to minor process and formulation changes.

## **HISTORY**

- ◆ 1897: Noyes and Whitney provided earliest reference to dissolution in an article entitled "The Rate of Dissolution of Solid Substances in Their Own Solution."
- ◆ 1934: Switzerland pharmacopoeia Helvetica was first regulatory body to introduce a disintegration test for tablets.
- ◆ 1950: Disintegration test became official USP method in USP XIV (14).
- ◆ 1970: First dissolution test appeared in USP XVIII (18).

## **FACTORS INFLUENCING DISSOLUTION RATE OF DRUGS FROM SOLID DOSAGE FORMS**

- ◆ According to the Noyes Whitney equation, the following factors affect dissolution of substances.
  - D = Diffusion coefficient
  - A = Surface area of substance
  - K = Partition coefficient of substance (water/oil)
  - H = Thickness of the stagnant layer
  - $C_s$  = Concentration of substances in the stagnant layer (a saturated solution around the solid particle)
  - $C_b$  = Concentration of the substance in the bulk phase of the solvent

Dissolution rate is the amount of active ingredient (s) in a solid dosage form dissolved in a unit of time under standardized conditions of liquid-solid interface, temperature and media composition. The dissolution rate is influenced by—

- ◆ Physicochemical properties of the pure drug (API)
- ◆ Physical characteristics of solid dosage form
- ◆ Wettability of the dosage form
- ◆ Penetration ability of the dissolution medium
- ◆ Swelling process
- ◆ Disintegration
- ◆ De-aggregation

## **EQUIPMENT – DISSOLUTION TESTER**

- ◆ Single station
- ◆ Six (6) stations
- ◆ Twelve (12) stations

## **DISSOLUTION TESTER COUPLED WITH UV/VIS SPECTROPHOTOMETER**

- ◆ A covered vessel
- ◆ A motor
- ◆ A metallic drive shaft
- ◆ A cylindrical basket (apparatus 1 as per USP and BP), a paddle from a blade, and shaft as stirring element (apparatus 2 as per USP and BP)
- ◆ A water bath (sink) or heated jacket capable of holding temperature at  $37^{\circ}\text{C} \pm 0,5^{\circ}\text{C}$
- ◆ The USP has apparatus 3, 4, and 5 for transdermal preparations and apparatus 6 and 7 for drug release

## **MEDIUM**

- ◆ Water
- ◆ 0.1m HCL
- ◆ Buffer (usually phosphate) pH 6.8 – 7.4 ( ± 0.05)
- ◆ 0.1m HCL + surfactants (usually 1% sodium lauryl sulfate)

## **PARAMETERS**

- ◆ Volume of medium and preparation (± 1%)
- ◆ Type of apparatus and speed
- ◆ Temperature (37 ± 0.50C)
- ◆ Time
- ◆ Sampling (midway between the surface of the dissolution medium and the top of the rotating basket or blade, and not less than 1cm from the vessel wall)
- ◆ Filtration (inert filters)
- ◆ Analysis (UV or HPLC)

## INTERPRETATION OF RESULTS

- ◆ BP – As per product's specification monograph or the general monograph on dissolution. (Not less than 70% of label claim in forty (40) minutes.)
- USP

## ACCEPTANCE TABLE FOR A UNIT SAMPLE

STAGE	NUMBER TESTED	ACCEPTANCE CRITERIA
S1	6	$Q + 5\%$
S2	6	12 units $(S1 + S2) \geq Q$ and no unit is less than $Q - 15\%$
S3	12	24 units $(S1 + S2 + S3) \geq Q$ , and not more than $2 < Q - 15\%$ , LIMIT $< Q - 25\%$

## ACCEPTANCE TABLE FOR A POOLED SAMPLE

STAGE	NUMBER TEST ED	ACCEPTANCE CRITERIA
S1	6	Average amount dissolved $< Q + 10\%$
S2	6	$(S1 + S2) \geq Q + 5\%$
S3	12	$(S1 + S2 + S3) \geq Q$ .

- ◆ Q is the amount of dissolved active ingredient specified in the individual monograph, expressed as a percentage of the labeled content.

## **EQUIPMENT CALIBRATION**

- ◆ RPM – A well-calibrated tachometer
- ◆ Temperature – a well-calibrated thermometer
- ◆ Time – standard clocks
- ◆ Disintegrating (M) and non-disintegrating mode (O) mode calibration as per USP
- ◆ Lot O – USP RS salicylic acid tablets 300mg
- ◆ USP RS salicylic acid powder
- ◆ Lot M – USP RS prednisone tablets 10mg
- ◆ USP RS prednisone powder

