REGULATORY ISSUES
FOCUS: REGISTRATION, THE ASAQ EXPERIENCE

John H. Amuasi (Bsc. MBChB. MPH.)
Ag. Head, R&D Unit
Komfo Anokye Teaching Hospital
Kumasi, Ghana

amuas001@umn.edu

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DNDi
Drugs for Neglected Diseases *initiative*

The mandate of the WHO Intergovernmental Working Group

WHA 59.24 (May 2006)

"*to draw up a global strategy and plan of action in order to provide a medium-term framework*" with the ultimate goal of "*securing an* ***enhanced*** *and* ***sustainable basis for needs-driven, essential health research and development*** *relevant to diseases that disproportionately affect developing countries,* ***proposing clear objectives and priorities for research and development****, and* ***estimating funding needs in this area*****".**

The 8 key elements of the Plan of Action

- Prioritizing R&D needs
- Promoting research and development
- Building and improving innovative capacities
- Transfer of technology
- Management of intellectual property
- **Improving delivery and access**
- Ensuring sustainable financing mechanisms
- Establishing monitoring and reporting systems

Pharmaceutical, Medical and Health-related Government and Regulatory Bodies around the world (I)

- Medicines and Healthcare Products Regulatory Agency (MHRA)
- The Food and Drug Administration (FDA)
- EMEA - The European Agency for the Evaluation of Medicinal Products
- FDB – The Food and Drugs Board

A directory of links to pharmaceutical, medical and health-related government and regulatory bodies around the world.

http://www.pharmweb.net/pwmirror/pwk/pharmwebk.html

Pharmaceutical, Medical and Health-related Government and Regulatory Bodies around the world (II)

- Mainly national agencies
- Often supported by strong legislature (Acts of Parliament)
- Major responsibility is to assure safety, efficacy and quality of foods, dietary supplements, drugs, psychotropic substances, vaccines, biological medical products, blood products, medical devices, radiation-emitting devices, veterinary products, nacortics, household hazardous substances, cosmetics, etc. (List varies)
- The assurance in safety, efficacy and quality of drugs is accomplished by two main processes i.e. pre-marketing control and post-marketing control/surveillance.

Important Issues to Consider (I)

- Drug registration is a continually evolving process and is becoming technically more complicated.
- The pressure on drug registration becomes evermore intense. The legal requirements change on a near daily basis and the technical demands for registration constantly increase.
- The evolution of the electronic submission means that in the future the whole registration procedure will eventually be entirely electronic.

Important Issues to Consider (II)

- It should not be underestimated how a mistake in the registration process can block a drug from reaching the shelves for months or even years.
- Valuable time is easily lost which is something no one can afford looking at the global burden of disease and today's highly competitive global markets.
- A lot of time can be lost when registering a drug because of a lack of optimal coordination among different departments. For instance the pharmaceutical development or the delivery of the clinical trials reports may not be according to schedule.

Often a tortuous process

- **Before registration**
- **Strategy-related tasks**
- **During registration**
- **After registration**

Drug registration system

There are 3 broad steps under the modern drug registration process namely:

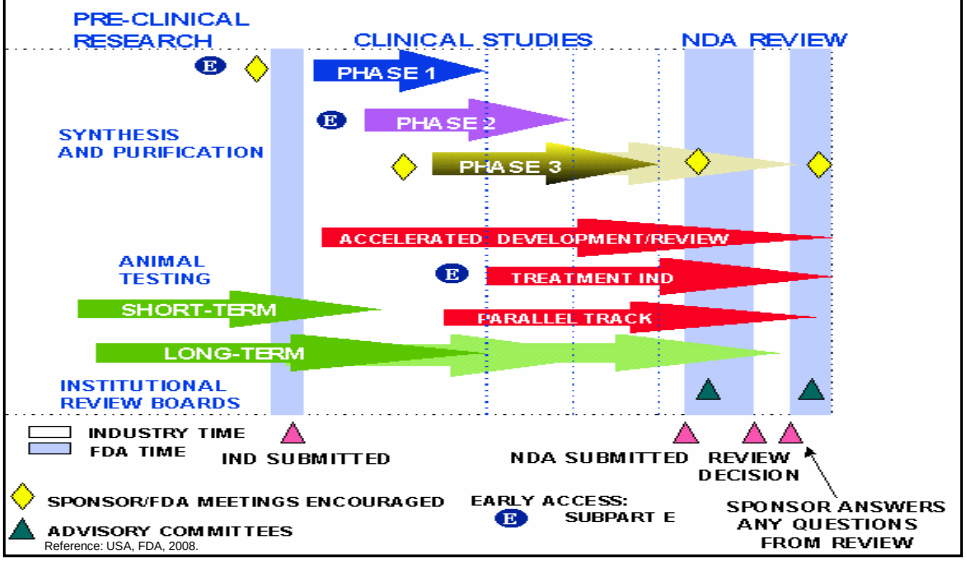
- Application for the permission to manufacture or import the drug sample.
- Application for the approval of drug quality and analytical control method.
- Application for the granted drug registration certificate.

In some parts of the world, drug registration is divided into 2 categories : modern drug and traditional drug.

key steps In the drug approval process (FDA - USA)

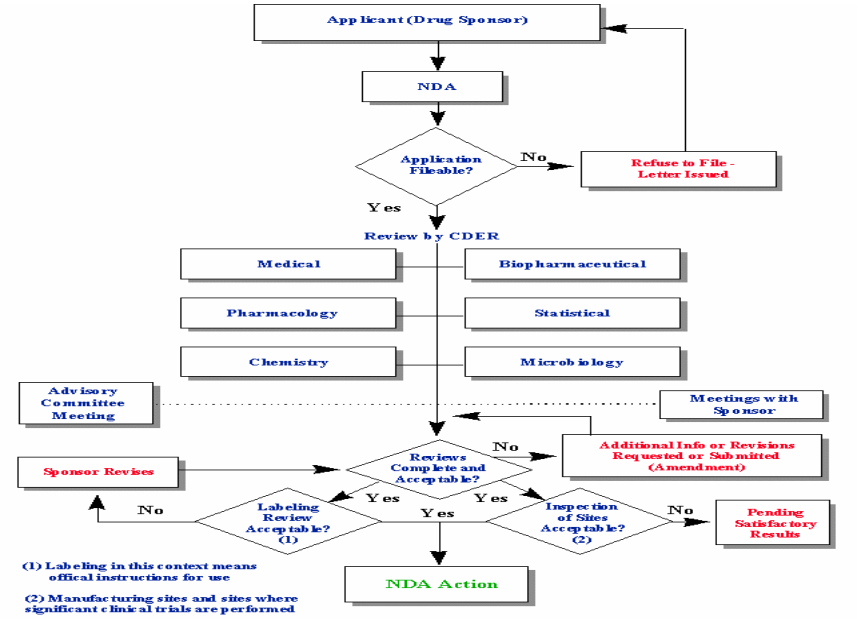
- Synthesis & Purification
- Animal Testing (short term)
- Animal Testing (Long-term)
- Institutional Review Boards.
- Phase 1 Clinical Studies.
- Phase 2 Clinical Studies.
- Phase 3 clinical studies.

The New Drug Development Process: Steps from Test Tube to New Drug Application Review



Reference: USA, FDA, 2008.

New Drug Application (NDA) Process



Reference: USA, FDA, 2008.

INTRODUCTION TO THE FIXED-DOSE ARTSUNATE-BASED COMBINATION THERAPY (FACT) PROJECT

- FACT project: Promotes antimalarial treatment policy changes and development of adapted drug combinations.
- Managed by the DNDi. Clinical studies coordinated and funded jointly by the DNDi and the WHO/TDR.
- Manufacturing, registration and distribution of AS/AQ to the public, and also the private markets by Sanofi-aventis
- Developed fixed dose combinations of Artesunate/Amodiaquine (AS/AQ) & Artesunate/Mefloquine (AS/MQ)

DNDi's FACT Malaria Project

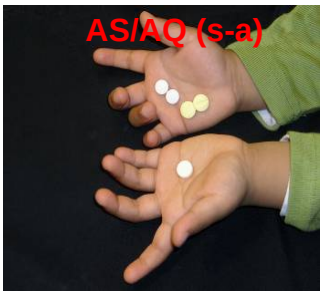
Objectives

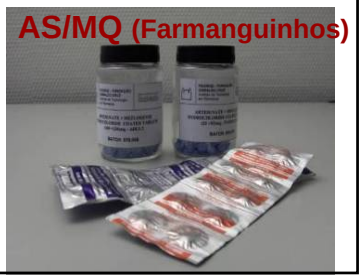
- Easy to use products:

- fewer tablets in regimen
- paediatric dose
- ensure drugs are taken **together** and **in correct proportions** (compliance)

– **Affordable**

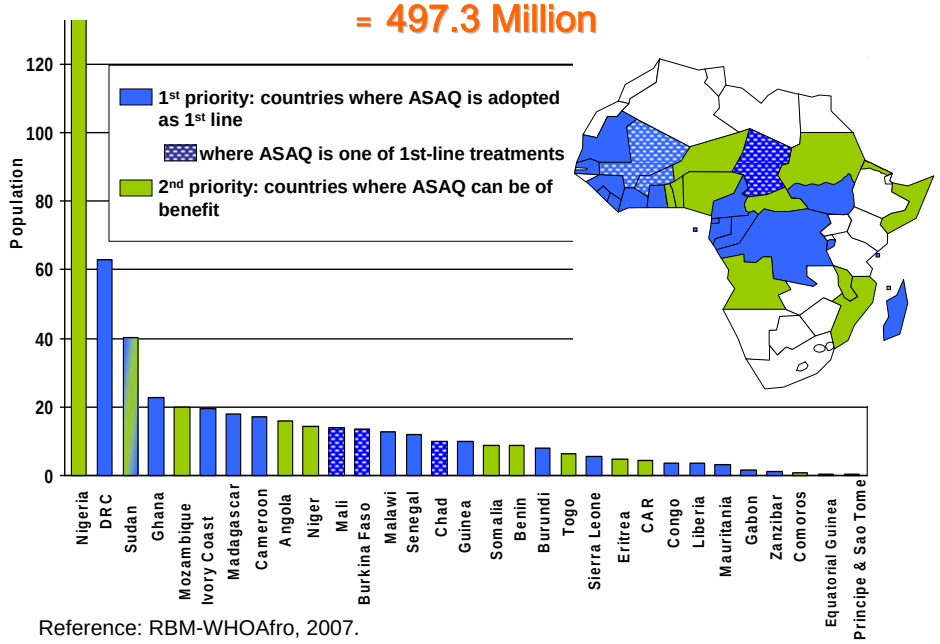
– **Available** as **public goods**





Reference: DNDi,, 2007.

Population which could benefit from ASAQ = 497.3 Million



Reference: RBM-WHOAfro, 2007.

The DNDi - Sanofi-aventis partnership

- An innovative partnership; no patent protection was sought. DNDi licensed ASAQ to s-a in Dec 2004
- Non-exclusivity; a marketing authorization will enable third parties to submit simplified applications for a generic version of AS/AQ.
- AS/AQ is being provided under the brand name Artesunate-Amodiaquine Winthrop® (ASAQ) at cost price – no-profit-no-loss price) to the public market in malaria endemic countries.
- Also available as Coarsucam™ for the private market at prices adapted to local markets, and Coarsucam™ Impact Malaria (no-profit-no loss price) for Sanofi-aventis “Access Card Program pharmacies.
- This tiered form of pricing is aimed at protecting the different antimalarial markets, while offering uniform quality of the same drug. It can be described as a “one drug, two prices, three packaging” arrangement.

Sanofi-aventis' role

In order to facilitate the registration process, Sanofi-aventis had to conduct/sponsor a number of clinical studies including:

- One each in phase I: Bioavailability of the Fixed Combination of Amodiaquine and Artesunate Under Fed & Fasted Conditions.
- One in phase III: ATAQ EASY: Artesunate + Amodiaquine Fixed Dose Combination in the Treatment of Uncomplicated Plasmodium Falciparum Malaria.
- Two in phase IV:

a.) Arsucam® (Artesunate + Amiodaquine) Efficacy and TOLerance (ATOL)

b.) ACT MALI: Treatment of Malaria Based on Combination Therapies.

Overview of ASAQ's registration

- **Feb '07 - Drug registered in Morocco, site of production facility**
- **Feb '07 - WHO prequalification dossier submitted**
- **As of June '07, approved in 14 countries**

The FACT project's approach to registration (I)

FACT project was an “unusual” project for various reasons:

- Neither AS nor AQ has been registered for use in the West.
- AS and AQ have been widely used in humans - especially in Africa and SE Asia.
- Based on this DNDi opted to use “established use principle.”

The FACT project's approach to registration (II)

- Earlier regulatory strategy: initial registration in Europe, and simultaneous submissions in the target endemic countries.
- Following partnership, regulatory strategy was changed to accelerate filing and availability of the product in endemic countries in Africa.
- Sanofi-aventis: Registration in Morocco and in disease-endemic countries.
- Sanofi-aventis: WHO prequalification, based on WHO’s ample regulatory documentation on artesunate and on amodiaquine: Arsumax® is already WHO pre-qualified.

The FACT project's approach to registration (III)

- Sanofi-aventis' choice to register in Morocco with DNDi's support met with some criticism,
- "Some" were "concerned" that an inferior regulatory process was being pursued.
- DNDi strongly rejected any suggestion that quality registration could only take place in the West.
- Same product, but two different names to the AS/AQ formulation, separate registration files had to be created.
- Coarsucam™ is considered by Sanofi-aventis as the parent drug, and Winthrop® as the generic.
- Registration process with the Moroccan drug regulatory authorities started in December 2005, and marketing authorisation was granted for Coarsucam™ on February 1, 2007. The Winthrop® file was approved on 18th June 2007

The FACT project's approach to registration (IV)

- The plant in Morocco is expected to soon have GMP certification. The site was visited by WHO inspectors in mid-June with no critical findings.

- With the GMP certification will come the opportunity for African governments to purchase Winthrop® from Sanofi-aventis using monies from the Global fund.

Important points to note from the ASAQ registration

- Need to bridge the gap between R&D for neglected diseases in academic setting and that in the pharmaceutical industry setting.
- Communication must be encouraged between academic researchers, researchers in industry, and regulatory authorities.
- There is the need for PDPs like DNDi to involve industry at an early stage during drug development projects so that major studies are conducted according to regulatory authorities' standards, which ultimately benefit the patients by saving both cost and time to market.
- There is a need for sustained engagement of regulatory authorities. Early involvement has the potential to save time and cost in the registration process.

Worth noting!

It is exciting to observe the positive "domino effect" that the launch of AS/AQ by the DNDi FACT team and Sanofi-aventis had on the pricing of other WHO recommended artesunate combination therapies worldwide. In a bid to rival the Sanofi-aventis price of <US$ 1.00 per adult treatment with AS/AQ, Novartis announced an immediate and significant reduction in the average price of its antimalarial medicine Coartem® (also an ACT) for the public market from US$ 1.57 to US$ 1.00 per treatment through an internal subsidy.