Pharmaceutical registration in Africa
Meeting new challenges

Dr Javier Guzman
Director of Research
Health Policy Division
The George Institute for International Health
DNDi Bi-Annual Meeting, Nairobi
24 June 2009

THE GEORGE INSTITUTE
for International Health

Outline

- Project brief: new challenges
- Regulatory overview
- Product registration challenges
  - Novel neglected disease drugs and vaccines
  - New FDCs and formulations for the developing world
  - Clinical trials of new neglected disease products
  - Generics
  - Global drugs
  - Non-novel vaccines
- Proposals
- Action map

THE GEORGE INSTITUTE
for International Health

The project brief: New challenges

- Regulatory functions are inter-dependent and any analysis should be integrated and contextualized across all functions
- There is only one Medicines Regulatory Authority (MRA)

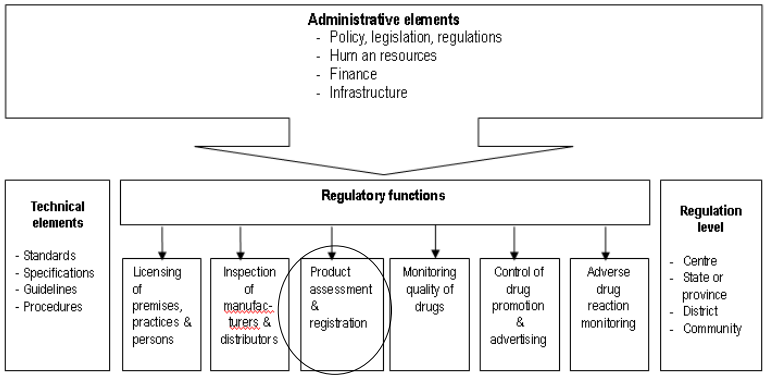
BUT the focus of this study is new challenges for product registration:

- African pharmaceutical regulatory capacity is under new strains
  - Key Western regulators (FDA, EMEA) have decreased supervision of products for export rather than domestic use
  - More products being developed specifically for African markets (e.g., ACTs; rotavirus vaccine; microbicides)

African regulators faced with "world first" review, approval or registration of products and product trials

THE GEORGE INSTITUTE
for International Health

Regulatory overview: Functions of Medicines Regulatory Agencies



Source: Modified from RatanawijitrasinWondemagegnehu 2002, 12.

THE GEORGE INSTITUTE
for International Health

African Medical Regulatory Authorities

WHO estimated that in 2004:

- 90% of African MRAs lacked capacity to carry out medicines regulatory functions
- > 40 African MRAs were largely non-functional

Why?

- Lack of clear legislative framework
- Dispersion of regulatory responsibility
- Lack of resources
- Lack of experienced and qualified staff
- Lack of political support
- Lack of appreciation for importance of medicine regulation

"Everything is designed to delay getting products where they are needed most."

THE GEORGE INSTITUTE
for International Health

Challenge 1: Novel neglected disease (ND) drugs and FDCs

Examples:

- Malaria vaccines
- Sleeping sickness drugs
- TB drugs
- HIV/AIDS vaccine

THE GEORGE INSTITUTE
for International Health

Initiatives to build and supplement capacity to register novel ND drugs in Africa

1. New pathways:
   - EMEA Article 58
   - Parallel Western and DC approval
   - Twinned Western and DC approval
   - First approval by a DC regulator

2. Western regulatory approval
   - Standard
   - Orphan
   - FDA expedited approvals

THE GEORGE INSTITUTE
for International Health

New pathways: Article 58

EMEA's Article 58

- Mechanism established by the European Commission in 2004 to facilitate developing country registration of medicines used to prevent or treat diseases of major public health interest including neglected infectious diseases

Pros

- Stringent EMEA-standard assessment + significant developing country input
- Factors in risk/benefit analysis relevant to endemic countries
- Very quick

Cons

- This is a scientific opinion to support developing country MRAs decisions (not a registration)
- Of virtually no interest to industry therefore few applications made
- Misunderstanding has led to concerns about 'double standards'

THE GEORGE INSTITUTE
for International Health

New pathways: Western/ DC approvals

- Parallel Western and DC approval
  - Intramuscular paromomycin for the treatment of visceral leishmaniasis
- Twinned Western and DC reviews (but not final approvals)
  - Artesunate-amodiaquine training dossier
  - RTS,S malaria vaccine trials
  - Conjugate meningitis A vaccine trials
- First approval by a DC regulator
  - Novel ARVs FDCs (India)
  - Conjugate meningitis A vaccine (India)
  - Artesunate-amodiaquine (Morocco)
  - Artesunate-mefloquine (Brazil)

THE GEORGE INSTITUTE
for International Health

Western MRA approval: Standard (1)

- Neglected disease product (e.g Coartem) is reviewed as any other product
- Expert opinions in areas where Western MRAs have less experience are commonly recruited

Pros

- Strong regulatory experience
- Industry interest as it provides access to developed and developing country markets (e.g. pneumonia vaccines)

Cons

- Unfamiliarity with the disease, products and end-users
- No obligation to request clinical trial data that may be vital for safe use in Africa
- Risk/benefit analysis will differ from Africa (e.g. rotavirus vaccine)
- May require costly trials in own jurisdictions, even if not relevant for use in Africa

THE GEORGE INSTITUTE
for International Health

Western MRA approval: Standard (2)

- Orphan approval
  - Primarily designed for Western diseases
  - 325 products (10 for neglected diseases: 4 for malaria, 4 for tuberculosis and 2 for kinetoplastids) approved by FDA as of May 2008
  - Little or no innovative value
- Expedited approvals

	Accelerated Review	Priority Review	Fast Track
Qualifying criteria	- serious or life-threatening illness - potential to address unmet medical need - Adequate and well-controlled studies supporting the use of surrogate outcome	- major advance in treatment or treatment where no adequate therapy exists	- serious or life-threatening condition - potential to address unmet medical need
Benefit during development	Adjusted trial outcome requirements	n.a.	Close communication with FDA
Benefit during review	n.a.	Additional attention, expedited review	Rolling review
Post-approval requirement	Studies to extend results from surrogate to clinical outcome	n.a.	n.a.

Source: Modified from Thaul S (2008) CRS Report for Congress. FDA Fast Track and Priority Review Programs. Fayetteville: The National Agricultural Law Center. Available: http://www.nationalaglawcenter.org/assets/crs/RS22814.pdf

THE GEORGE INSTITUTE
for International Health

Challenge 2: Generic drugs in Africa

- Most common product for registration, both locally manufactured and imported from other DC manufacturers
- Relatively simple assessment (quality, therapeutic equivalence)

BUT …..

- Lowest safety net (usually no prior approval by stringent MRA)
- Many African MRAs cannot effectively evaluate generic drug dossiers
  - Unable to assess bioequivalence locally
  - Unable to perform GMP inspections of non-domestic manufacturers

THE GEORGE INSTITUTE
for International Health

Initiatives to build and supplement capacity to register generics and FDCs

- FDA "tentative approval" and PEPFAR
- WHO drug prequalification programme
- West African Drug Regulatory Authorities Network (WADRAN)

THE GEORGE INSTITUTE
for International Health

WHO drug prequalification

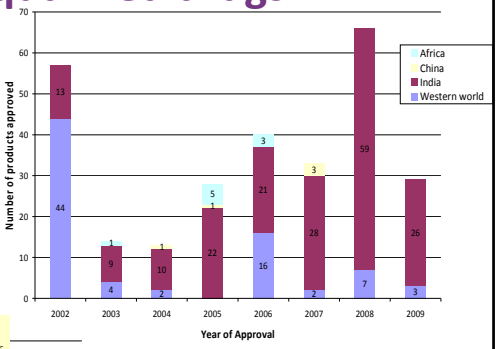
- "Surrogate" regulatory approval created in 2001
- 280 drugs prequalified as of 2 June 2009
- Precondition for procurement through multilateral initiatives (e.g. Global Fund, AMFm)

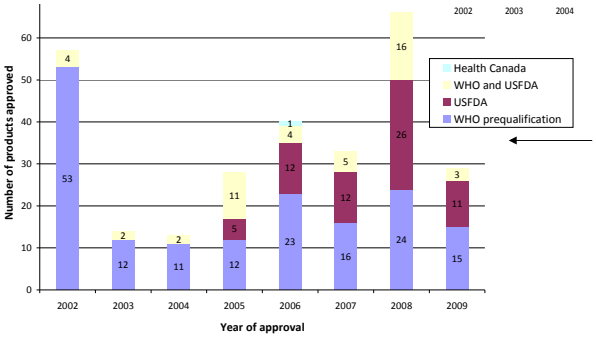
- Certain diseases and product types predominate:
  - HIV (241 or 86%), TB (20 or 7%) and malaria (16 or 6%)
  - Generic drugs (56%) and new fixed-dose combinations (21%) – just over ¾ of all approvals
  - Mostly from DC producers

THE GEORGE INSTITUTE
for International Health

WHO pre-qualified drugs

By geographical location of manufacturing source





By approving regulatory agency

THE GEORGE INSTITUTE
for International Health

FDCs & new formulations

Different products present different levels of challenge:

Similar to generic difficulty:

1) FDC is an exact copy of existing FDC (e.g Cipla's version of GSK's Lamivudine+Zidovudine -Combivir)

2) FDC combines existing single products but in the same doses (e.g DOTS)

Similar to novel product difficulty:

3) FDC combines existing single products but in a new dosage or formulation (e.g Cipla's Lamivudine/Nevirapine/Stavudine)

4) FDC includes completely novel product/s (e.g. known artemisinin + newly discovered anti-malarial compound)

Requirement	1	2	3	4
Bioavailability data	Not usually	Not usually	Sometimes	Yes
Bioequivalence data	Yes	Yes	Sometimes	Sometimes
Preclinical pharmacology and safety	Not usually	Not usually	Sometimes	Yes
Clinical safety and efficacy	Not usually	Not usually	Yes	Yes

THE GEORGE INSTITUTE
for International Health

Challenge 3: Clinical Trials in Africa

- Increased product CT applications in past 5 -10 years
- BUT 84% of African countries unable to satisfactorily authorise CTs in 2005

Why?

- Lack of clear legislative framework for CT conduct and regulation
- Unclear delineation b/w roles of ethical review boards and MRAs
- Lack of skills to review and approve applications

THE GEORGE INSTITUTE
for International Health

Initiatives to build and supplement clinical trial regulatory capacity

- WHO, PATH Malaria Vaccine Initiative and GSK
  - Seven African MRAs and the Belgian MRA (the country where the vaccine was manufactured) reviewed and approved the phase III trial design for RTS,S.
- The Gambia, Mali, Ghana, Senegal:
  - Joint review of PATH's conjugate Meningitis A vaccine clinical trial application
- African Vaccine Regulatory Forum (AVAREF)
  - Designed for novel DC vaccines
  - Includes regulators and ethics boards from 19 African countries
- Developing Country Vaccine Regulator Network (DCVRN)
  - Coordinated by WHO to improve regulation of vaccine trials and review of trial data
  - But only one African member (South Africa)

THE GEORGE INSTITUTE
for International Health

'Global' disease drugs in Africa

- Non-communicable diseases such as hypertension, diabetes and cancer that affect populations in every part of the world.
- Less pressing issue since most are first registered in the West, therefore African MRAs can build on external findings

Key challenges for African MRAs are:

- Extracting the regulatory info they need (different formats; diff't requirements)
- Conducting the crucial additional local risk/benefit assessment

THE GEORGE INSTITUTE
for International Health

Non-novel vaccines in Africa

- A couple of b/ground lines on vaccines; where from; edl etc.;
- African MRAs fully rely on the WHO prequalification system

WHO vaccine prequalification system

- Set up in 1987 as a service to UNICEF and other UN vaccine procurement agencies
- Initial evaluation of vaccines is conducted by the MRA in the country of manufacture which must be competent in the six core vaccine regulatory functions as identified by WHO
- Role of WHO prequal incl. cap bldg

THE GEORGE INSTITUTE
for International Health

Overarching issues

Coordination of capacity building initiatives

- Lack of coordination e.g. between dossier assessment training
- Conflict between initiatives e.g. EMEA's Article 58 and EMEA's orphan drug legislation
- Gaps
  - capacity building and support services focussing heavily on regulatory approvals
  - limited attention for other general regulatory activities
- Drug vs vaccine prequalification

Regional regulatory harmonisation

- Ongoing discussion for many years but
  - top-down approaches
  - Unfeasible expectations
  - Lack of trust
  - Disparate legislative frameworks
  - National sovereignty imperative
  - Lack of funding

THE GEORGE INSTITUTE
for International Health

Regional regulatory harmonisation (positive developments)

- Bottom up approaches
  - The African Drug Registration Harmonisation consortium led by NEPAD, the Pan African Parliament (PAP), BMGF, DFID, the Clinton Foundation and WHO (Feb 2009 meeting)
- African policy makers set the agenda and drive its progress
  - Southern African Development Community (SADC)
  - Economic Community Of West African States (ECOWAS): WADRAN
  - East African Community (EAC)
  - *"While efforts are made to harmonise medicines regulation in the region, they should at the same time be geared towards assisting countries with limited resources to build their regulatory capacity as this will be the foundation for building trust among different MRAs and eventually lead to mutual recognition of regulatory decisions."*

THE GEORGE INSTITUTE
for International Health

Some proposed initiatives

THE GEORGE INSTITUTE
for International Health

Improving efficiency and quality of novel neglected disease drug registration

Short-term low-cost supplementary capacity

- No Western review without formal DC input
- Automatic WHO prequalification of products given a positive opinion under Art. 58
- Improve Article 58's attractiveness to product developers
  - Allowing a positive Art.58 opinion to provide automatic EU Orphan approval OR
  - Allowing a positive Art.58 opinion to be converted to EMEA approval with a single European bridging study

Longer-term capacity building

- Regional Centres of Regulatory Excellence (case study)

THE GEORGE INSTITUTE
for International Health

Improving efficiency and quality of generic registration

Short-term low-cost supplementary capacity

- Automatic WHO prequalification of generic drugs approved by stringent MRAs
- 'Outsource' some WHO prequalifications to stringent MRAs
- Centralised up-to-date database of positive plant inspections by WHO and stringent MRAs
- WHO to conduct a strategic review of WHO drug prequalification priorities to identify priority diseases to be included in the programme

Longer-term capacity building

- Support and encourage African Regional Economic Communities (e.g WADRAN, SADC, EAC) to set up regional drug bioequivalence testing centres
- Regional Centres of Regulatory Excellence (case study)

THE GEORGE INSTITUTE
for International Health

Improving efficiency and quality of clinical trial regulation

- Regional Centres of Regulatory Excellence (case study)
- Implement existing proposals for African sub-regional clinical trial registers (West Africa, Southern Africa, East etc),
  - Possibly building on existing registers e.g. the South African register
- WHO to develop boilerplate legislation to support MRA regulatory functions in African countries that do not yet have legislation in place

THE GEORGE INSTITUTE
for International Health

Improving efficiency and quality of novel 'global' drug registration

- Automatic reciprocal WHO prequalification of innovator drugs
- WHO to agree on a set of reference MRA's, whose decisions can reliably be leveraged by African MRAs
- WHO to develop model regulatory packages for Abridged Review and Verification. Until then, WHO to fund centralize collation and re-formatting regulatory decisions from reference MRAs
- Develop a risk-benefit management checklist to review evaluations done by other MRAs
- Regional Centres of Regulatory Excellence

THE GEORGE INSTITUTE
for International Health

Improving efficiency and quality of vaccine registration

Short-term low-cost supplementary capacity

- Reciprocal recognition by WHO prequal of vaccine approvals by reputable reference MRAs
- WHO to develop a model "fast-track" regulatory package, which could be used by African MRAs to locally register WHO prequalified vaccines

Longer-term capacity building

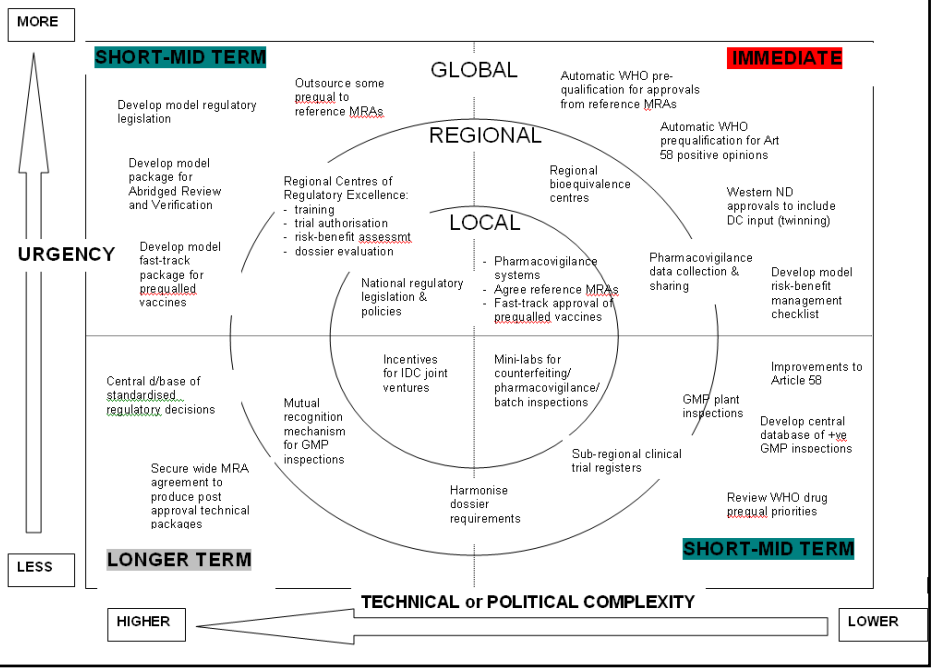
- Centres of Regulatory Excellence (case study)

THE GEORGE INSTITUTE
for International Health

Prioritising capacity building initiatives

THE GEORGE INSTITUTE
for International Health

A capacity building map



Centres of Regulatory Excellence (1)

- One bricks-and-mortar centre in each of Africa's main sub-regions
- Built on existing regional regulatory initiatives where possible

Two objectives:

- To develop African capacity in the mid-to-long term to conduct all regulatory activities
  - Platform for training regulatory fellowships
- To provide a regional resource to support MRAs in the short-to-mid term to conduct challenging regulatory tasks

THE GEORGE INSTITUTE
for International Health

Centres of Regulatory Excellence (2)

- Product registration activities
  - Participate in review of novel ND products by external agencies as well as joint regional review of dossiers
  - Conduct joint review of novel ND products in conjunction with stringent external regulatory authorities –twinning-
  - Improve registration of generics and simple FDCs by
    - conducting joint GMP plant inspections at the regional level,
    - supporting regulatory staff to participate in external generic assessments by WHO Prequalification and PEPFAR,
    - conducting regional review and approval of dossiers for generics and simple FDCs
  - Conduct localised risk-benefit analysis on dossiers of global products approved by external reference MRAs
- Clinical trial regulation and training activities

THE GEORGE INSTITUTE
for International Health