REGISTERING NEW DRUGS: THE AFRICAN CONTEXT

New tools for new times

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OUTLINE

- Background
- Regulatory pathways used to register neglected disease products
  - Western regulatory approval
  - Neglected disease specific pathways
  - Alternative regulatory pathways
- African regulatory advances
- Recommendations

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BACKGROUND

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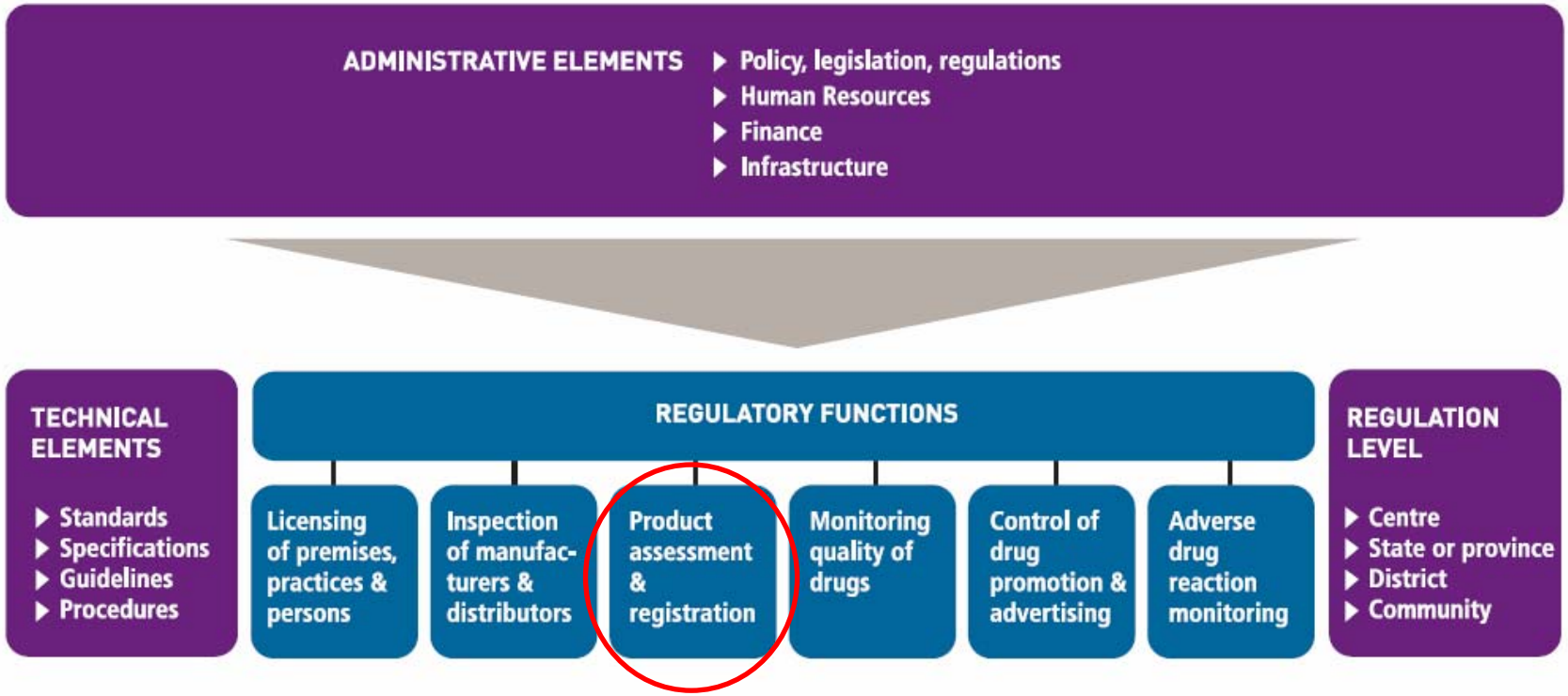
Functions of Medicines Regulatory Agencies

Regulatory functions are inter-dependent and any analysis should be integrated and contextualized across all functions



Source: Modified from Ratanawijitrasin/Wondemagegnehu 2002, 12.

THE PROJECT BRIEF: NEW CHALLENGES

BUT this study is on new challenges for product registration of new drugs:

- African MRAs have traditionally focused on generics; relied on Western MRAs for review of innovator products

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

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

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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

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Regulatory pathways used to register novel neglected disease drugs in Africa

1. Western regulatory approval
   - Routine regulatory approval
   - Orphan Drug Legislation
   - Expedited approvals
2. Neglected disease specific pathways
   - EMEA Article 58
   - WHO prequalification
   - US FDA “tentative approval” and PEPFAR
3. Alternative regulatory pathways
   - Parallel Western and DC approval
   - Twinned Western and DC approval
   - First approval by a DC regulator
   - WHO vaccine prequalification

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WESTERN REGULATORY APPROVAL

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ROUTINE WESTERN APPROVAL

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

Pros

- Strong regulatory experience
- Clear protocols and rules, liability management
- Industry interest as it provides access to developed and developing country markets (e.g. pneumonia vaccines)

Cons

- Delayed access for target patients in Africa
- Inability to provide clear guidance on clinical trial design
- Lack of sufficient safety and efficacy data requirements for wider use
- Inappropriate data requirements (e.g. product trials in US jurisdictions where disease barely occurs)
- Inappropriate risk-benefit assessment for DC use

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OTHER WESTERN PATHWAYS

ORPHAN DRUG APPROVAL

- Primarily designed for rare Western diseases
- 325 products approved by FDA as of May 2008 (10 for neglected diseases: 4 for malaria, 4 for tuberculosis and 2 for kinetoplastids)

Pros

- ODL research grants
- Tax breaks
- Free scientific advice

Cons

- Can be approved without large-scale clinical trials
- Incentivises less valuable health innovations (H*alf of 10 neglected disease products approved by FDA until May 2008 had little or no innovative value)*

EXPEDITED APPROVALS

- Accelerated approval (US FDA)/ Conditional approval (EU EMEA)
- Priority review (US FDA)/ Fast Track (EU EMEA)
- Fast Track (US FDA)

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NEGLECTED DISEASE SPECIFIC PATHWAYS

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ARTICLE 58

- Established by European Commission in 2004 to facilitate developing country registration of medicines to prevent or treat diseases of major public health interest including neglected infectious diseases
- Scientific opinion to support developing country MRA decisions, not a formal registration

Pros

- Stringent EMEA-standard assessment
- Significant structured developing country input
  - Factors in risk/benefit analysis relevant to endemic countries; formally includes WHO expertise
- Very quick – average 2.5 months from submission to assessment
- Does not require European data
- WHO involvement in review process facilitates approval at DC country level

Cons

- Lack of incentives for companies (no reason to use this mechanism)
  - No ODL-like benefits or access to European market
- Poorly understood, poorly positioned and lacks good advocates

WHO drug prequalification (1)

- "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

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WHO drug prequalification (3)

By disease category

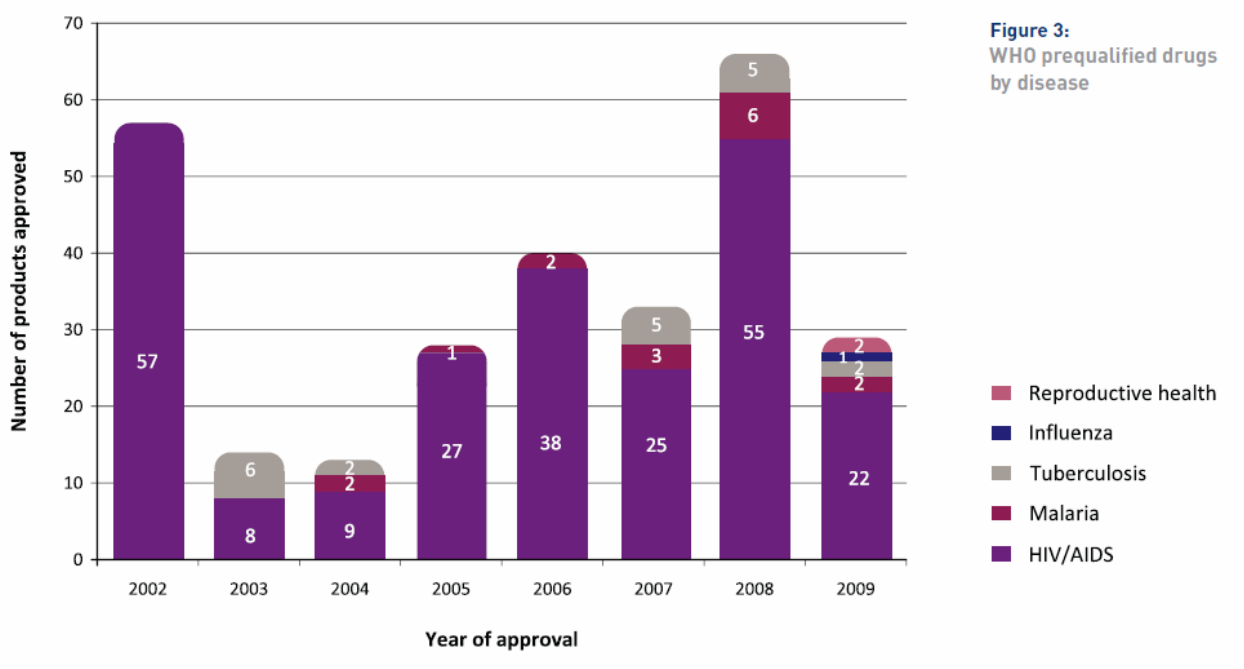

Figure 3:
WHO prequalified drugs by disease

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WHO drug qualification (2)

By approving regulatory agency →

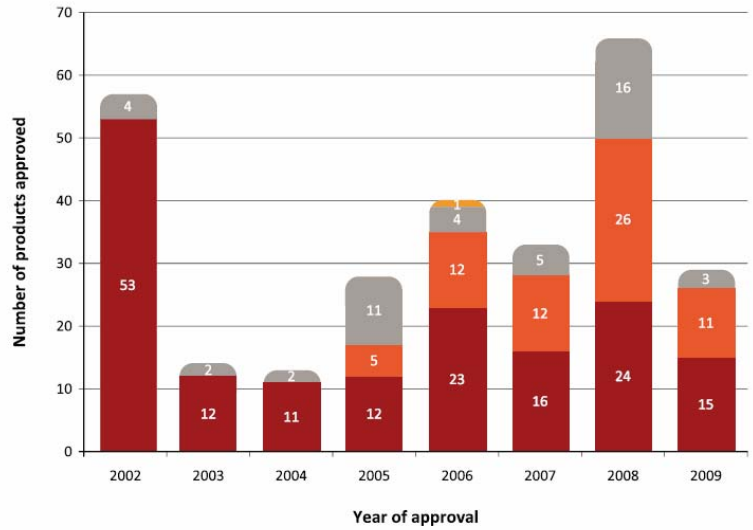

Figure 1: WHO pre-qualified drugs per year by regulatory agency[19]

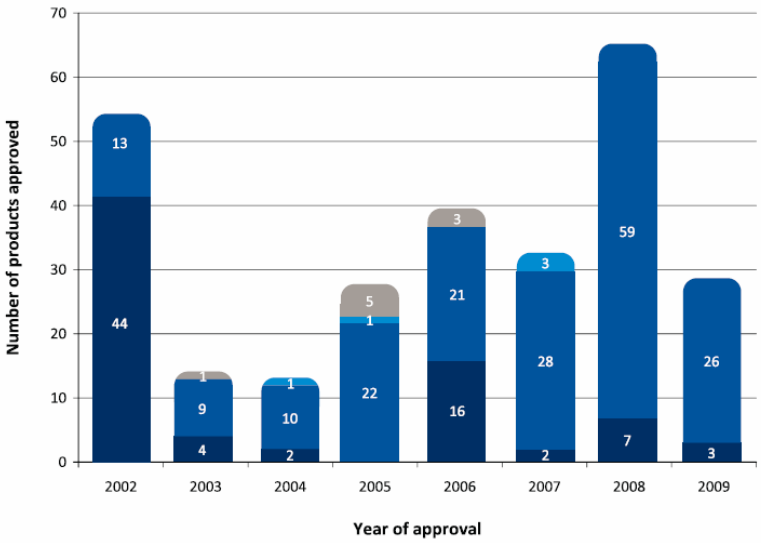

Figure 2: WHO pre-qualified drugs by geographical location of manufacturing source*

← By geographical location of manufacturing source

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WHO drug prequalification (4)

Pros

- Provides generic manufacturers with assistance in dossier prep, scientific advice
- No application fee
- Wide range of capacity building activities
- Quality standards similar to FDA and EMEA

Cons

- Mostly only drugs for HIV, malaria and TB, with majority generic HIV drugs
- Slow; average 2 years due to voluntary, no-fee, capacity building approach
- Lack of resources
- Pulling together multi-country teams for each review inefficient, expensive
- Concern about over-reliance of African regulatory system on WHO Prequal

FDA “tentative approval” and PEPFAR

- For HIV drugs purchased with PEPFAR funds for use outside US
- As of June 2009,100 products have been fully or tentatively approved in association with the PEPFAR program; of which71 have been generics and 29 have been new products
  - 22 of the 29 new products are new combinations or regimens not previously authorised in the US
  - 7 are paediatric reformulations
- Main drawback: not designed for innovator products / only for HIV drugs

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ALTERNATIVE REGULATORY PATHWAYS

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

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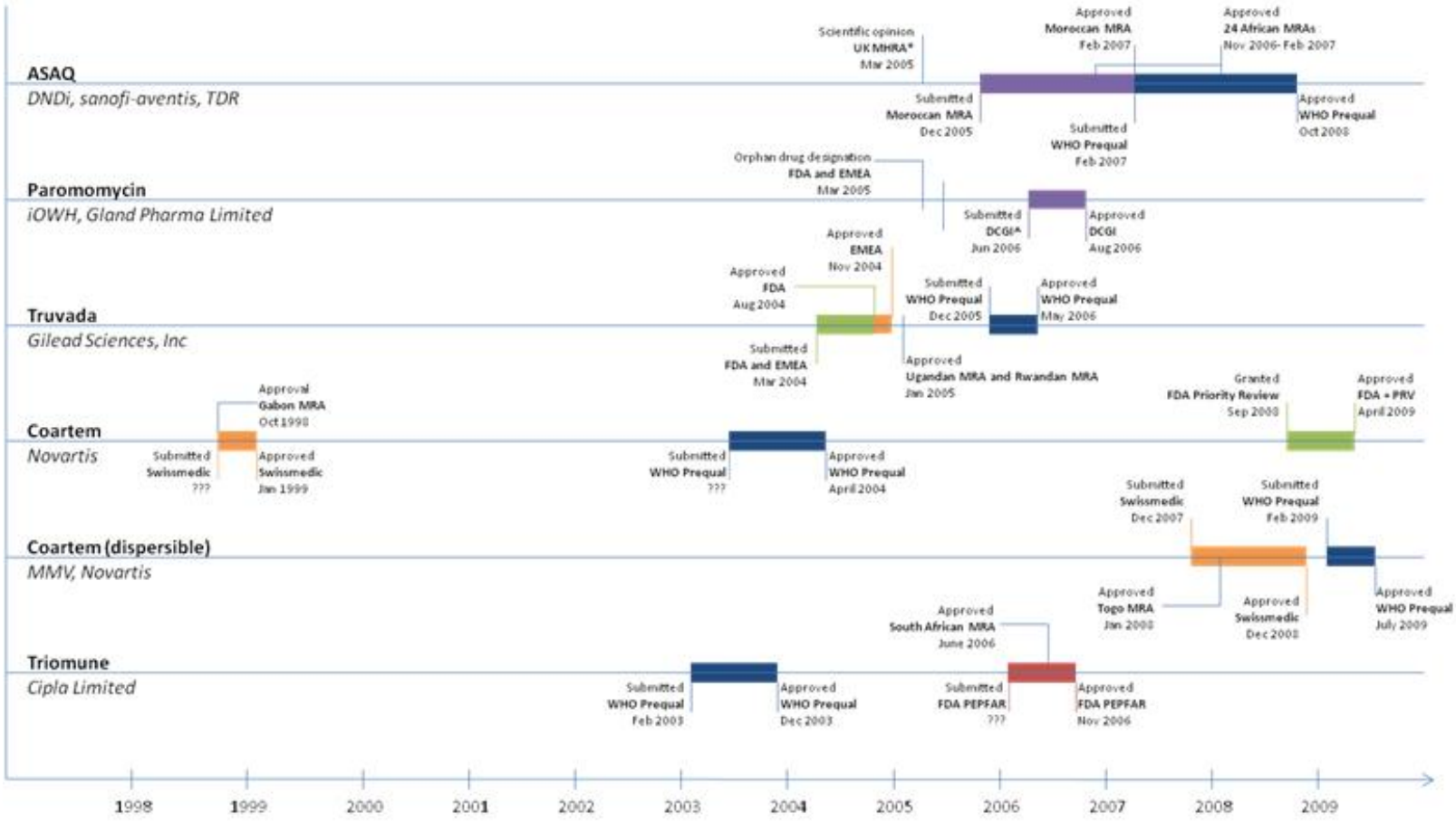
CURRENT SITUATION



*UK Medicines and Healthcare products Regulatory Agency
*Drugs Controller General of India

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AFRICAN REGULATORY ADVANCES

- **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)** – created legally enforceable framework for regional cooperation, including pharmaceutical business plan for 2007-2013
  - **Economic Community of West African States (ECOWAS)** – WADRAN created as forum for drug regulatory authorities
  - **East African Community (EAC)** – seeks to harmonise drug registration procedures w/o preventing movement of pharma products

Summary of performance/ gaps of each mechanism

	Safety, efficacy, quality assessment	Assesses suitability for Africa	Systematic DC input	Expedites access	Resource-efficient	Builds African capacity
Twinned approval	✓✓	✓✓	✓✓	✓✓	✓✓	✓✓
Article 58	✓✓	✓✓	✓	✓		✓
WHO drug and vaccine prequalification	✓✓	✓✓	✓			✓
Parallel approval	✓✓	✓✓	✓		?	✓
Routine and expedited Western approval *(Fast-track, priority review, standard review)*	✓	?				
Orphan approval	✓	?				
First approval by DC regulator	?	✓	✓✓	✓✓	✓	
Accelerated review	?	?		✓		

? *Signifies that the mechanism's delivery against that criterion must be assessed on a case-by-case basis*

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RECOMMENDATIONS

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Aims

- To address the drawbacks of individual regulatory mechanisms for new neglected disease (ND) drugs
- To move towards a more integrated system for approval of new ND drugs
- To build African capacity to regulate new ND drugs

Improving regulatory efficiency in the short-term (1)

Recommendation 1. Formal twinned review: all regulatory reviews of novel neglected disease drugs by stringent MRAs (including article 58 and WHO prequal) to formally include regulators from endemic countries targeted for that product

- Benefits:
  - Addresses lack of Western expertise
  - Formal not ad-hoc DC expert input (more efficient)
  - Builds DC regulatory skills

Recommendation 2. Automatic WHO prequalification for novel ND products approved by stringent MRAs

- Benefits:
  - Expands scope of WHO prequal to more diseases of DC relevance
  - Allow many more products to be prequalled each year
  - Expedites African access to new medicines (no sequential review)
  - Integrates national and international mechanisms

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Improving regulatory efficiency in the short-term (2)

Recommendation 3. Improve Article 58's attractiveness to product developers by :

- Automatic WHO prequalification of drugs given positive opinion under Article 58
- A positive Article 58 opinion to be converted to EMEA approval with a single European bridging study *OR*
- A positive Article 58 opinion to provide automatic EU Orphan approval
- Benefits:
  - Encourages drug developers to use Article 58 rather than less DC-sensitive regulatory pathways
  - Expedites African access to new medicines
  - Integrates regional and international mechanisms

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Improving regulatory efficiency in the short-term (3)

Recommendation 4. Select experienced Western MRAs to conduct prequalifications on behalf of, and in addition to, WHO

- Western MRA responsible for dossier assessment; and overall management of the process/ WHO liaises with manufacturers to improve dossiers as needed (supported by Western MRA)
- Benefits:
  - Allow many more products to be prequalled each year
  - Expedites African access to new medicines
  - Integrates national and international mechanisms

Recommendation 5. WHO to conduct a strategic review of WHO drug prequalification priorities, along the lines of SAGE reviews for vaccines, including working with African MRAs and Ministries of Health to identify priority diseases or areas to be included in prequalification (and/or outsourced to reference MRAs)

- Benefits:
  - Expands scope of WHO prequal to more diseases of DC relevance

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Building and supporting African regulatory capacity (1)

Recommendation 6. Fund Centres of Regulatory Excellence in each of Africa's main sub-regions: West, South, East, Central and North Africa.

The Centres would provide regulatory skills and efficiencies to support African MRAs in:

- meeting their immediate regulatory challenges (short-term)
- building and retaining African regulatory capacity by providing a pathway for professional training (mid-to-long term)

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Thank you

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Building and supporting African regulatory capacity (2)

Recommendation 6 (cont'd)

The Centre's activities could include:

- Joint regional review of product dossiers (with external support as necessary)
- Joint GMP plant inspections at the regional level
- "Twinning", i.e. formal participation in external regulatory reviews such as FDA PEPFAR-linked reviews, EMEA Article 58 assessments, WHO Prequalification etc
- Clinical trial regulation, including joint review and approval
- Training and regulatory fellowships

Benefits:

- Builds DC regulatory skills
- Integrates national, regional and international mechanisms
- Expedites African access to new medicines
- Decreases time and cost to developers of new ND products
- Addresses lack of Western expertise
- Formal not ad-hoc DC expert input (more efficient)

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A CAPACITY-BUILDING ACTION MAP