Ensuring quality, safety and efficacy of vaccines

Vaccine regulatory issues in African countries

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Outline of the presentation

1. Issues and challenges met by regulatory systems in Africa
2. WHO policy to ensure quality, safety and efficacy of vaccines
3. Activities planned and implemented to address the above issues
4. Monitoring, progress and impact on vaccine regulatory systems
Issues & challenges met by regulatory systems in Africa: Scientific issues

- Limited expertise in new vaccines science (Combo, DNA, adjuvant, preservative, vector, etc.)
- Huge viral diversity (HIV, Rotavirus) & complex geographic distribution
- Weak registration & licensing process when dealing with biologicals
- Inadequate immune response to natural infection
- Immune correlates of protection difficult to establish
- Vaccine response is not always better than natural infection
- Lack of appropriate models indicating that human trials are key to develop research
- Definition of efficacy and end points are key in clinical trial protocol
Issues & challenges met by regulatory systems in Africa

Regulatory issues
- No/weak regulations or not consistent with international standards (lot release, GMP, GCP, GLP, etc)
- Overlap of roles of parties (NRA & Ethics)
- Limited knowledge of foreign sponsored regulations
- Absence of provision for expedite reviews
- Regulation/Guidelines in place require updating (article 58, ECBS guidelines)
- No inspection of clinical trials sites
- Lack of procedures to assess, authorize and monitor CTs
- Limited/no Pharmacovigilance & laboratory capacity

Managerial issues
- Limited human resources for regulation
- Lack of funding to develop NRA oversight
- No or limited local manufacturing capacity
- Limited exchange or sharing regulatory information to guide decision making
- Sponsors and manufacturers influence decision making that is not consistent with international standards
FUNCTIONNAL NRA THAT HAVE CAPACITY TO REGULATE VACCINES, AFRICA, July 2006

- Functionnal NRA
- Potential to become functionnal
- Limited or weak vaccine regulatory system

Countries shown:
- Algeria
- Egypt
- Ghana
- Morocco
- Nigeria
- Senegal
- South Africa
- Tunisia
- Uganda
- Zimbabwe

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Assured quality source of vaccine procured through WHO prequalification, 2006

14 industrialized countries
- Australia
- Belgium
- Canada
- Denmark
- France
- Germany
- Hungary
- Italy
- Japan
- Rep.Korea
- United Kingdom
- USA
- Switzerland
- Sweden

13% population

6 developing countries
- Brazil
- Bulgaria
- Cuba
- India
- Indonesia
- Senegal

24% population

24 manufacturers

65 pre-qualified vaccines used in 112 countries

53% total population
Main source of vaccines used for national immunization programmes in Africa, 2006

Only Y.Fever is produced, all other vaccines are procured through UNICEF

Source of vaccines, 2006

Number of countries
Total = 46 countries

- UN agency: 27 countries (57%)
- Procuring: 19 countries (41%)
- Producing: 1 country (2%)

15 out 19 countries are procuring from a country that have functional NRA

92% countries used vaccines of assured quality

Using WHO Prequalification scheme

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Using WHO Prequalification scheme
2. WHO policy to ensure quality, safety and efficacy of vaccines
Definition of “Assured quality vaccines” for a vaccine producing country

- National Regulatory Authority (NRA) independent from vaccine manufacturer & or procurement system
- NRA fully functional (system + 6 regulatory functions implemented)
- No unresolved reported problem with vaccine

Guided by Experts Committee on Standardization of Biologicals (ECBS) recommendations on safety, efficacy and quality issued in WHO Technical Report Series (TSR)

Ensure that “100%” of vaccines used in all national immunization programmes are of assured quality
Vaccine regulatory process

Pre-marketing phase
- Licensing/Registration= evaluation process
  - Applicants
    - Dossier (manufacturer or distributor)
  - Product Evaluation
    - Dossier
    - Quality
    - Safety
    - Efficacy
  - Laboratory access
  - Authorization clinical trials
    - (Ethical review process, compliance against GLP,GMP,GCP)

Post Marketing phase
- Marketing Authorization (M.A.)
  - Post marketing AEFI surveillance
  - Post market distribution
  - Lot release
  - Inspections
    - testing
  - Regulatory inspections
  - Licensing facility
  - Authorization clinical trials
  - Market distribution
  - Dossier
    - Applicants
      - Dossier (manufacturer or distributor)

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## National Regulatory Functions recommended for vaccine development

<table>
<thead>
<tr>
<th>Regulatory functions</th>
<th>UN agency</th>
<th>Procure</th>
<th>Produce</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Regulatory system</strong></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Marketing Authorization &amp; Licensing activities</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Postmarketing: AEFI</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Lot release</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Laboratory access</td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Regulatory inspections</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Authorization &amp; monitoring of CTs</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

- Functions undertaken in producing Countries with functional NRA
- Functions in countries that conduct clinical trials

CTs: Clinical trials, UN: United Nations, AEFI: Adverse Events Following Immunization
The Global Training Network (GTN) trained 1200 staff from 100 countries since 1996 & was supported by WB, JICA, DFID, AusAid, WHO, EU, IDB, ADB, UNICEF, WHO + EDCTP

Courses
1 - Regulatory inspections
2 - Quality Control Methods
3 - Laboratory Quality Systems
4 - vaccine regulation
5 - Animal Husbandry
6 - Short Course in DTP
7 - Lot Release and Lab Access
8 - Post marketing surveillance/AEFI
9 - Licensing (for procuring countries)

Participants
1. NRA Staff with Government Plan
2. Staff of Manufacturer with NRA & Strategic Plan
3. NRA Staff and EPI Staff from vaccine procuring countries (for AEFI course only)
4. Activities planned and implemented
By end of 2010: 37 out of 46 COUNTRIES
WILL HAVE DEVELOPED APPROPRIATE CRITICAL
REGULATORY FUNCTIONS

2006: 6 countries
2007: 6 countries
2008: 8 countries
2009: 8 countries
2010: 9 countries

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## Activities recommended to strengthen vaccine regulatory systems in Africa

<table>
<thead>
<tr>
<th>Sensitization of country Stakeholders</th>
<th>Networks &amp; Forum to Exchange and share Regulatory information</th>
<th>Training on critical regulatory functions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Development of Institutional Development Plan (IDP)</td>
<td>Development regulation &amp; procedures</td>
<td>Joint review of clinical trials applications</td>
</tr>
<tr>
<td>Joint inspection of Clinical trials sites</td>
<td>NRA assessment &amp; Follow up visits to monitor impact</td>
<td>Building centre Excellence &amp; roster of regulatory/scientific experts</td>
</tr>
</tbody>
</table>
**ACTIVITIES TO STRENGTHEN VACCINE REGULATORY SYSTEMS IN AFRICA**

<table>
<thead>
<tr>
<th>Activities conducted</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Fund raising plan</td>
<td>Completed</td>
</tr>
<tr>
<td>2. Three NRA planning workshops countries with IDP* for 28 countries</td>
<td>Completed</td>
</tr>
<tr>
<td>3. Meeting of Developing Countries vaccines regulatory network (DCVRN)</td>
<td>Completed</td>
</tr>
<tr>
<td>4. Joint review of CTs applications for MeningoA + Workshop on regulatory procedures for clinical evaluation of vaccines + forum for the evaluation of clinical data of rotavirus vaccines for registration purposes</td>
<td>Completed</td>
</tr>
<tr>
<td>5. Sensitization/advocacy workshop for all country stakeholders</td>
<td>1 out 3 completed</td>
</tr>
<tr>
<td>6. GTN training provided to AFR countries on vaccine regulation</td>
<td>9 out of 28 countries completed</td>
</tr>
<tr>
<td>7. GTN Training provided to AFR countries on PMS/AEFI</td>
<td>15 out of 28 completed</td>
</tr>
<tr>
<td>8. GTN training provided to AFR countries on clinical evaluation</td>
<td>6 out of 28 completed</td>
</tr>
</tbody>
</table>

* Institutional Development Plan (IDP)
NRA PLANNING WORKSHOPS
CONDUCTED TO DEVELOP INSTITUTIONAL DEVELOPMENT PLAN (IDP) FOR 28 COUNTRIES IN 2005

Funded by
WHO & AAVP

Addis Abeba, Jan.2005

Ouagadougou, May 2005

Gaborone, Dec.2005

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AFR : Regional initiatives 2004-2007
Objectives & expected outcome

1. Planning NRA activities through development of Institutional Development Plan: completed in 28 countries
2. Promote communication among NRAs and raise awareness on regulatory changes and challenges: DCVRN input, AVAREF, Joint review, Joint inspection of CTs, Sensitization workshops (Uganda)
3. Promote communication between sponsors/regulators/ethics committees/ research centres to determine specific needs for different types of vaccines: same as point 2
4. Provide expert support to assess suitability of clinical data for registration: DCVRN, AVAREF, training on clinical evaluation
5. Facilitate capacity building activities and availability of expertise for regulatory review of clinical trial applications and monitoring of clinical trials: NRA assessment, follow up visits, meeting of regulators and training on relevant regulatory functions, joint review of CTAs, joint inspection, AVAREF
6. Plan and organise training on relevant regulatory functions that are critical for African NRAs: Clinical evaluation, PMS/AEFI and regulation. DCVRN on regulatory inspections of CTs
WHO/EDCTP activities planned & conducted to support the development of an harmonized regulatory framework in Africa, 2005-2007 - **PLANNING PHASE: 2005**

1. Jan, May and Dec.: 3 NRA planning workshops for 28 countries (Addis, Ouagadougou & Gaborone):
   - **Main outcome**: 28 Institutional Development Plans (IDP) to implement harmonized/common regulatory framework to ensure quality, safety, efficacy of vaccines and relevant clinical trials conducted in Africa.

2. March: training course on authorisation/approval of clinical trials (Pretoria, South Africa)
   - **Main outcome**: Providing knowledge to regulators and vaccine experts about principle of vaccine clinical evaluation relevant to authorisation and monitoring of clinical trials
   - **Countries involved**: Ghana, the Gambia, Uganda, Kenya, Nigeria & Ethiopia. WHO funding
WHO/EDCTP activities planned & conducted to support the development of an harmonized regulatory framework in Africa, 2005-2007 - **PLANNING PHASE: 2005**

3. **Sept. 2005**: Workshop on Regulatory Procedures for clinical evaluation of Vaccines (Addis, Ethiopia)
   1. **Main outcome**: Templates procedures for submission/review clinical trials applications and integration of activities & importation/release of clinical batches
   2. **Countries involved**: Botswana, Ghana, Cameroon, Ethiopia, The Gambia, Uganda, Kenya, Mali, Nigeria, Senegal, Tanzania, Zambia, South Africa. WHO funding

4. **Dec. 2005**: Regulatory forum on clinical evaluation of rotavirus vaccines (Botswana 12/05)
   1. **Main outcome**: a) Presentation & discussions of scientific information on issues that may affect the efficacy and safety of rotavirus vaccines. B) allow countries to make a final decision with regards to registration of rotavirus vaccines
   2. **Countries involved**: Botswana, Ghana, Gambia, Zimbabwe, Malawi, Cote d'Ivoire, South Africa, Zambia, and Cameroon: WHO funding
WHO/EDCTP activities planned & conducted to support the development of an harmonized regulatory framework in Africa, 2005-2007 - IMPLEMENTATION PHASE 2006

1. **Jan-May:** EDCTP/WHO agreement developed & signed
   1. **Main outcome:** Support of 360.000 Euros for 18 months. (June 2006-Dec.2007)
   2. **Countries involved:** Ghana, Uganda, Tanzania, Nigeria, Malawi, The Gambia, Mozambique, Rwanda, Gabon, Mali, Burkina Faso, Kenya, Ethiopia, Zambia, Cote D'Ivoire, EDCTP funding

2. **June:** Joint review of CTA of Conjugate Meningitis A vaccine (Banjul, The Gambia)
   - **Main outcome:** Review of clinical trials application for phase II Conj:Menin.A vaccine by Mali & the Gambia national regulatory & vaccine experts on relevant gaps/missing information concerning Men.A vaccine Clinical trials.
   - **Country involved:** The Gambia, Mali, Ghana, Senegal.- WHO funding

3. **July & August:** Country workshop in Uganda & Senegal to sensitize all stakeholder for implementation of IDP recommendations:
   - **Main outcome:** Updated IDP and coordination plan to involved all stakeholders in follow up implementation of recommendations
   - **Country involved:** Senegal & Uganda - WHO funding

2006

1. Sept.: AFRO Vaccine Regulatory Forum AVAREF (Accra, Ghana, 19-22 Sept) - EDCTP funding - completed
2. Development & translation of training material for the Benin (French) and Ethiopian (English) courses on authorisation & monitoring of clinical trials - completed

2007

1. Jan.2007: Joint inspection of CT of Conjugate meningo A vaccine - EDCTP funding
2. March 2007: Workshop on regulatory inspections of clinical trials (tentative) - EDCTP funding
3. April & Oct.: AVAREF meeting
5. Feb & June 2007: Training for 20 countries (english speaking) on authorisation & monitoring of CTs (Addis, Ethiopia) - EDCTP funding
6. Jan-Dec: Follow up IDP and monitoring activities in 5 countries
4. Progress and impact on vaccine regulatory systems
Country Status:

0 NRA assessment conducted as of 1998

Country status: NRA assessment conducted & planned

- NRA assessment conducted
- Not yet conducted
- To be completed in 2006 however NRA pre-screening already completed

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68 NRA assessments conducted (Oct. 1998-Dec 2005)

Country status: NRA assessment conducted & planned

- NRA assessment conducted
- Not yet conducted
- To be completed in 2006 however NRA pre-screening already completed

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220 Regulatory experts recruited
(Oct. 1998 – April 2006)

NRA regulatory experts

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CHANGES DOCUMENTED TO IMPROVE REGULATORY OVERSIGHT OF VACCINES

1. Plan planned and implemented for all countries involved
2. Training planned and conducted for all countries involved
3. Template procedures to evaluate CTs applications
4. Amended regulation to involve NRA in evaluation of CTs
5. Clarification of roles/responsibilities to authorize CTs
6. Focal point & training requested for staff
7. Guidelines discussed, amended for endorsement by MoH
8. Coordination among NRA/Ethics Committee to authorize CTs
9. 1st African Vaccine regulators forum (Ghana, Accra, Sept.2006)
1st AVAREF meeting, Sept. 2006
African Vaccine Regulators Forum

- **Participants:** 19 Countries, NRA and Ethics committee
- **Experienced NRAs:** EMEA & US FDA
- **Product sponsors:** GSK, MVPPATH, WRAIR, US NIH
- **Themes:** selected disease of importance: HIV, malaria, Menigo A & Rotavirus, regulators
- **Funded by:** WHO, EDCTP; MVPATH and AAVP
- **Issues:** Low funding for NRAs, conflict of interest because of limiting resources, lack of confidence in IRBs, separate institutions, access epidemiological data, laboratory capacity, ADR investigation, information sharing network

**Recommendations:**
- Need to expand and sustain capacity building in vaccine trials oversight
- Joint review of clinical trial application should be expanded
- Strong interest in conducting joint inspection of clinical trials sites
- Increase training opportunities to develop regulatory capacity
- Develop guidance for clarification roles of NRA & ethics committees
- Pharmacovigilance provision re article 58 should be flexible for implementation
- Develop clinical trials case definition of efficacy for malaria vaccines
- Secretariat's forum is hosted in WHO/AFRO
Next steps…

- Plan for the 2nd phase and identify resources to sustain WHO/EDCTP initiative (initial phase granted 300,000 Euros to be completed by Dec. 2007)
- Support in priority coordination and monitoring of initiative (forum, networking, African experts in regional coordination mechanism/institutions)
- Support training, coordinate curriculum development and expand to all relevant institutions (NRA, Ethics, Research, Pharmacovigilance centre)
- Expand networking among key networking international leader and country partners
- Use and expand IT to advocate, publish best practices, experience and develop online training
Information sources for regulators

www.who.int

www.sharepoint.who.int/ATT (access upon request, used as space to share information with all country participants and partners (eg. EDCTP, UNICEF, NRAs, NCLs, Ethics, etc)