Regulatory Science Workforce Needs to Support Therapeutics Development for Global Neglected Diseases

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Aeras
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### PDPs work across different diseases and modalities

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Microbicides &amp; preventatives</th>
<th>Therapeutic product</th>
<th>Diagnostics</th>
</tr>
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<tbody>
<tr>
<td>Aeras</td>
<td>PATH</td>
<td>PATH</td>
<td>FIND</td>
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<tr>
<td>CD4</td>
<td>PATH</td>
<td>PATH</td>
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<td>GATB</td>
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</table>

- **HIV/AIDS**
- **TB**
- **Malaria**
- **NTD²**
- **Diarrhea³**
- **Respiratory**

**Aeras**: Aeras Global TB Vaccine Foundation  
**CD4**: Diagnostics  
**DNDi**: Drugs for Neglected Diseases Initiative  
**FIND**: Foundation for Innovative New Diagnostics  
**GATB**: Global Alliance for TB Drug Development  
**HHVI**: Human Hookworm Vaccine Initiative  
**IAVI**: International AIDS Vaccine Initiative  
**IDRI**: Infectious Disease Research Institute  
**IOWH**: Institute for One World Health  

**IPM**: International Partnership for Microbicides  
**IVCC**: Innovative Vector Control Consortium  
**IVI**: International Vaccine Institute  
**MMV**: Medicine for Malaria Venture  
**MVI**: Malaria Vaccine Initiative (PATH)  
**MVP**: Meningitis Vaccine Program (PATH)  
**PDVI**: Pediatric Dengue Vaccine Initiative  
**PATH VAC**: PATH’s Vaccine Development Program

1. PVS Includes Rota Vaccine Program (RVP), Pneumo Vaccine Project (PVP), Enteric Vaccine Initiative (EVI), Influenza Vaccine Development Program (IVDP)
2. Includes HAT, visceral leishmaniasis, chagas, hookworm, and dengue 3. Includes cholera, typhoid, and rotavirus

FDAs List of Tropical Diseases that Qualify for PRVs

- Tuberculosis
- Malaria
- Blinding trachoma
- Buruli Ulcer
- Cholera
- Dengue/Dengue haemorrhagic fever
- Dracunculiasis (guinea-worm disease)
- Fascioliasis
- Human African trypanosomiasis
- Leishmaniasis
- Leprosy
- Lymphatic filariasis
- Onchocerciasis
- Schistosomiasis
- Soil transmitted helminthiasis
- Yaws
In interviews PDP senior leaders suggested a range of functions where collaboration would be beneficial.

- **Regulatory** (18 mentions)
- **Clinical site sharing** (15 mentions)
- **Access** (15 mentions)
- **Policy** (13 mentions)
- **Advocacy / communications** (12 mentions)
- **Business development** (10 mentions)
- **Clinical site development** (10 mentions)
- **Manufacturing** (8 mentions)
- **Fundraising** (7 mentions)
- **Financial allocations / budgeting** (6 mentions)
- **Data management** (6 mentions)
- **Admin / G&A** (4 mentions)
- **Adjuvants** (4 mentions)
- **CROs** (4 mentions)
- **Access to compounds** (3 mentions)
- **Meetings to share knowledge** (3 mentions)
- **Investment cases** (3 mentions)
- **Epidemiological research** (2 mentions)
- **Statistics** (2 mentions)
- **Toxicology** (2 mentions)
- **Procurement** (2 mentions)
- **Laboratories** (2 mentions)
- **Relationships with industry** (2 mentions)

**Initial prioritization of design teams based on**
- Input from interviewees
- Existence of other initiatives in the area
## Time for Response to Phase I Submission

<table>
<thead>
<tr>
<th>Country</th>
<th>Scientific Review</th>
<th>Ethics Committee Review</th>
<th>Regulatory Review</th>
<th>GMO Review</th>
<th>Import Permission Issuer</th>
<th>Total time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brazil</td>
<td>RA</td>
<td>National and local</td>
<td>RA</td>
<td>Yes</td>
<td>RA</td>
<td>1-9 months</td>
</tr>
<tr>
<td>India</td>
<td>Local scientific committee</td>
<td>National and local</td>
<td>RA</td>
<td>Yes</td>
<td>RA</td>
<td>31 months</td>
</tr>
<tr>
<td>Kenya</td>
<td>Local scientific committee</td>
<td>US and national</td>
<td>-</td>
<td>-</td>
<td>Pharmaceutical Dept</td>
<td>4-6 months</td>
</tr>
<tr>
<td>Mozambique</td>
<td>Investigator’s institution</td>
<td>National</td>
<td>MOH*</td>
<td>-</td>
<td>Pharmaceutics Dept,</td>
<td>6-7 months</td>
</tr>
<tr>
<td>South Africa</td>
<td>RA</td>
<td>National</td>
<td>RA</td>
<td>Yes</td>
<td>RA</td>
<td>4-6 months</td>
</tr>
<tr>
<td>Uganda</td>
<td>Local scientific committee</td>
<td>US and national</td>
<td>RA</td>
<td>-</td>
<td>Local scientific committee</td>
<td>4-5 months</td>
</tr>
</tbody>
</table>

*MOH = Ministry of Health
African Medicines Regulatory Harmonization
– a Bill and Melinda Gates Foundation Initiative

Resource restraints restrict regulatory function: limiting access to quality medicines
- 90% of African NRAs lack capacity to guarantee quality, safety and efficacy
- Sponsors face a landscape of disparate regulation and frequent delays
As a result – fewer drugs available in low income countries

AMRH – a platform to build African regulatory capacity

Capacity building across all regulatory functions: product types, clinical trials, processes

Streamlined functions: common requirements, dossiers, and inspections; resource pooling, work sharing,

Activities:
Regional agreements
Harmonize registration of generics
Expand to innovative medicines
Build all fundamental regulatory capabilities

Adapted from Vincent Ahonkhai, BMGF
## Clinical Trials & Approvals in countries w NTDs

<table>
<thead>
<tr>
<th>Issues for NRA</th>
<th>FDA Assistance</th>
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</thead>
<tbody>
<tr>
<td>Lack of consistent review timelines</td>
<td>Training- risk management</td>
</tr>
<tr>
<td>Different Risk/Benefit issues</td>
<td>Share information - systems/processes</td>
</tr>
<tr>
<td>Critical trial issues</td>
<td>Joint reviews of clinical protocols</td>
</tr>
<tr>
<td>- trial site, population issues</td>
<td>Exchange programs</td>
</tr>
<tr>
<td>- need to focus on pivotal trials</td>
<td>Approval mechanism for NTD</td>
</tr>
<tr>
<td>- integrate new methods, eg EDC</td>
<td>Accept non US Clinical data</td>
</tr>
<tr>
<td>Lack of first time approval mechanism</td>
<td>Use endemic country experts on Adv Ctes</td>
</tr>
<tr>
<td>- easier to approve generics</td>
<td>Link approval to WHO prequalification</td>
</tr>
<tr>
<td>Safety review/pharmacovigilance</td>
<td></td>
</tr>
<tr>
<td>- lack of postmarketing surveillance</td>
<td></td>
</tr>
<tr>
<td>- assure continued quality</td>
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</table>
Medicines & Vaccines Prequalified by WHO
Status 2010

**MEDICINES**
- 252 Pre-qualified products
  - used in 20 countries

**VACCINES**
- 107 Pre-qualified vaccines
  - used in 124 countries
Regulatory Science Issues in countries w NTDs

Issues for NRA

- New product/approach for NTDs
- Lack of resources / scientific expertise
- Lack of CMC/GMP experience
- Product not approved by SRA

FDA Assistance

- Scientific advice on product [under IND]
  - EMEAs Art 58 Scientific Opinion
- Regulatory science/collaborations
  - Res. on NTDs; assay biomarker dev.;
  - Critical Path programs
- Mechanisms to share information
  - MOUs w low income countries
- Exchange programs
  - to and from FDA; sabbaticals
- Approve product for NTD
  - new Guidance Documents
FDA Guidance Documents for NTDs

- General Principles for the Development of Vaccines to Protect Against Global Infectious Diseases  
  issued September, 2008

  “FDA can license vaccines to protect against infectious diseases or conditions not endemic in the U.S.”

- Regulatory pathway same as for vaccines licensed for use in U.S.
- Encourages use of IND system for product and clinical review
- Clinical data from trials conducted outside the U.S. can be used for approval

  Draft August 2011

  “…considerable latitude to exercise its scientific judgement to determine the kind and quality of data and information ..required..to meet standards for approval”

  “FDA regulations..require that we consider the severity of disease and the absence of alternative therapy in weighing whether the benefits of therapy outweigh known and potential risks”

- FDA committed to facilitate access to therapies for NTDs
- there may be circumstances when one trial provides adequate evidence of efficacy
FDAs Critical Path Initiative – Support for developing TB products

TB Scientific Research Projects supported in 2010

- Development and validation of point of care tests for tuberculosis
  - University of Utah
- Small molecule biomarkers for tuberculosis treatment, relapse and cure
  - Colorado State University
- Development of a diagnostic for latent TB
  - University of Georgia Research Foundation
- Consortium for TB biomarkers
  - Global alliance for TB drug development
- Qualifying new pre-clinical models for TB drug development
  - Global alliance for TB drug development
- Discovery of biological and immunological biomarkers for TB vaccines
  - Aeras
Critical Path to TB drug Regimens Initiative

FDA Critical Path working together with TB Alliance and BMGF to accelerate the development of new TB combination drug regimens

[Diagram showing current and new combination approach paradigms]
Differences in Mtb Strains
- implications for medicines & vaccines

CBER/FDA lab shows different host Response to Mtb human isolate
Jeon, B et al Infec Immun 2008 76: 5173-80

Global Distribution of 6 Main Lineages of Mtb
- Varied genotype/phenotype
- Variable virulence/DR

Recommendations from PDP Survey:

**Regulatory Capacity Building**

- Establish structures for information sharing among regulators within regional settings
- Involve regulators from endemic countries more in assessment of new products
- Develop regional centers of excellence in regulatory science
- Build sustainable regulatory capacity in endemic countries (global shared vision); systematize training programs; exchange programs, etc

White paper: “Regulatory challenges in ensuring equitable access to new health products in low income countries” www.conceptfoundation.org/access.php
THE GLOBAL REGULATORY PATHWAY