The Role of Drug Regulatory Agencies
A view from the access perspective

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Agenda

• ... the angle of resource limited settings
  • Setting the stage
  • Access & factors influencing access
  • Current limitations
  • Forecast workload for DRA
  • Increasing capacities, maintaining access
    • Potential ways forward
Swiss Tropical Institute
Basel, Switzerland
Introduction to the Institute
Introduction to the Institute

Swiss Tropical Institute

Public Health & Epidemiology

Clinical and Diagnostic Services

Medical Parasitology & Infection Biology

Swiss Centre for International Health (SCIH)

Innovation

Validation

Application
Setting the stage
Drug regulation ensures that...

- Medicines are of the required quality, safety, efficacy
- Health / patients have the necessary information for rational use of medicines
- Medicines are appropriately manufactured, stored, distributed, dispensed
- Illegal manufacturing and trade are detected and adequately sanctioned
- Promotion and advertising is fair, balanced, aimed at rational drug use
- Access to medicines not hindered by unjustified regulatory work
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Access to interventions

Factors influencing access

• Depending on
  • Adequate R & D
  • Diagnosis
  • Reliable information
  • Quality of product
  • Availability
  • Affordability
  • Accessibility
  • Pharmacovigilance
## Access R&D for neglected diseases

<table>
<thead>
<tr>
<th>Drug</th>
<th>Year</th>
<th>Problem</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sleeping sickness</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pentamidine</td>
<td>1939</td>
<td>Limited efficacy against 2(^{nd}) stage, ADR</td>
</tr>
<tr>
<td>Suramin</td>
<td>1920</td>
<td>Limited efficacy against 2(^{nd}) stage, ADR</td>
</tr>
<tr>
<td>Melarsoprol</td>
<td>1949</td>
<td>Most severe ADR, treatment failures</td>
</tr>
<tr>
<td>Eflornithine</td>
<td>1980</td>
<td>Difficult application, ADR</td>
</tr>
<tr>
<td>Nifurtimox</td>
<td>1970</td>
<td>Not registered, severe ADR</td>
</tr>
<tr>
<td><strong>Chagas Disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nifurtimox</td>
<td>1970</td>
<td>Long treatment, ADR, limited efficacy against 2(^{nd}) stage</td>
</tr>
<tr>
<td>Benznidazole</td>
<td>1974</td>
<td>Long treatment, ADR, limited efficacy against 2(^{nd}) stage</td>
</tr>
<tr>
<td><strong>Buruli Ulcer</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td></td>
<td>Surgical intervention necessary</td>
</tr>
</tbody>
</table>
Access
Diagnosis
Access

Reliable information
Access

Drug quality
Access
Availability

For free is not cheap enough
J. Jannin, WHO
### Access Affordability

<table>
<thead>
<tr>
<th>Developed by</th>
<th>Drug name</th>
<th>Price (US $) / adult treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sanofi-Aventis</td>
<td>Paluther® (artemether IM)</td>
<td>24.65</td>
</tr>
<tr>
<td>GSK</td>
<td>Malarone® (atovaquone/proguanil)</td>
<td>12.00</td>
</tr>
<tr>
<td>GSK</td>
<td>Halfan® (halofantrine)</td>
<td>5.00</td>
</tr>
<tr>
<td>Sanofi-Aventis</td>
<td>Arsumax® (artesunate)</td>
<td>3.08</td>
</tr>
<tr>
<td>Roche</td>
<td>Lariam® (mefloquine)</td>
<td>2.60</td>
</tr>
<tr>
<td>Novartis</td>
<td>Coartem® (artemether/lumefantrine)</td>
<td>2.40</td>
</tr>
<tr>
<td><strong>Target price:</strong> US$ 1 per adult treatment**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMV-GSK *</td>
<td>Artekın® (DHA-piperaquine)</td>
<td>≤1.00</td>
</tr>
<tr>
<td>MMV-Shin Poong-Uni Iowa*</td>
<td>Pyronaridine/artesunate</td>
<td>≤1.00</td>
</tr>
<tr>
<td>DNDi-Sanofi Aventis*</td>
<td>Artesunate/amodiaquine</td>
<td>≤1.00</td>
</tr>
<tr>
<td>WHO/TDR-GSK</td>
<td>Lapdap® (chlorproguanil/dapsone)</td>
<td>≤0.29</td>
</tr>
</tbody>
</table>

Source: Moran 2005, New Landscape of Neglected Disease Drug Development
Access

Accessibility
Access Pharmacovigilance
From Efficacy to Effectiveness

Efficacy → 80%
X Access → 80%
X Targeting Accuracy → 80%
X Provider Compliance → 75%
X Consumer Adherence → 75%
= Effectiveness → 29%
Access
A Health System Problem
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  - Increasing capacities, maintaining access
    - Potential ways forward
Today’s approaches
Financial resources

- Mix of public funding with fees for services
  - Government resources very often insufficient
  - Fees may be a hindrance for drug importation

- Working example: Democratic Republic of Congo
  - Theoretical annual budget of DRC DRA: US$ 3 mio
  - Actual financing level: ~10%
  - Additional income through user fees
    - Preliminary approval license 1 yr: US$ 250 tax + 25% fees
    - License for 5 years: US$ 300 USD tax + 25% fees

- Difficult balance between insufficient funding & prohibitive fees in a very fragile market

Source: MPH Thesis T. Barth 2006, STI
Today’s approaches
Drug registration

• Working example: Democratic Republic of Congo

• Approach
  • Authorization of the country of origin required
    ➢ Country of origin = country of manufacturing

• Capacity
  • 1 position

• Duration
  • Between 1 to 3 months w/o fast-track

Source: MPH Thesis T. Barth 2006, STI
Today’s challenges
QA & Pharmacovigilance

• Working example: Democratic Republic of Congo

• Quality Assurance before market entry
  • Responsibility of the Division Quality Assurance
    • Very limited manpower
  • Mandated to external (Congolese) laboratories
    • No independent validation of test results

• Quality assurance after market entry
  • Task of the Centre of pharmacovigilance
  • Created in 2003
    • Partially operational: 1 coordinator, 1 data manager
  • 14 / 5500 MD’s willing to collaborate

Source: MPH Thesis T. Barth 2006, STI
Today’s challenges
Implementation of rules

- Common infringements
  - Lack of staff qualification
  - Illegal sales of unpackaged tablets
    - Painkillers & antimalarials
  - Illegal stocking of prescription only medicines
    - Lack of information at shop & district-level regulators
  - Stocking of unregistered imported drugs
  - Lack of valid permit
  - Lack of sanctions

- Private sector needs control
  - Rigorous handling of situation would impede access

Source: Goodman, Health Policy & Planning 1-11
Today’s challenges
Conduct of clinical trials

• Authorization to conduct clinical trials
  • Ethical review largely improved over past 3 years
  • Trials often conducted without competent review of DRA
  • Generally no inspections of clinical trials by DRA

  ➢ Competitive area
    • DRA has direct impact on attractiveness of country

• Working example Tanzania
  • Trial stopped by sponsor for safety concerns 14.03.2008
  • DSMB unblinding & review 02.05.2008, letter to TFDA 15.05.
  • Clearance to continue enrollment received 25.06.2008
  • Enrolment complete on 26.06.2008

  ➢ Difficult initial balance between sufficient control & adequate interference and response
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Increasing tasks for DRA
New drugs 1975 - 1999

1393 new chemical entities marketed

- Tropical diseases: 13
- Tuberculosis: 3

11.4% of total disease burden
1.1% of drugs

Increasing tasks for DRA
Funding the new collaboration

Source: Moran 2005, New Landscape of Neglected Disease Drug Development
Increasing tasks for DRA
First results of the new collaboration

Active Neglected Disease (ND) drug R&D projects by institution* (Dec 2004)

- 63 ND Drug Projects
- 3 new industry ND Institutes
- 18 drug project in clinical trials & 2 ND drugs in registration
- Projection 8-9 new drugs until 2010

Source: Moran 2005, New Landscape of Neglected Disease Drug Development

* Medicines for Malaria Venture (MMV), the TB Alliance, Drugs for Neglected Diseases initiative (DNDi) and the institute for One World Health (iOWH)
### Increasing tasks for DRA

**Epidemiological Transition**

<table>
<thead>
<tr>
<th>Cause low income countries</th>
<th>%</th>
<th>Cause developed world</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 HIV/AIDS</td>
<td>17.9</td>
<td>Ischemic heart disease</td>
<td>22.6</td>
</tr>
<tr>
<td>2 Lower respiratory infections</td>
<td>10.1</td>
<td>Cerebrovascular disease</td>
<td>10.7</td>
</tr>
<tr>
<td>3 Malaria</td>
<td>9.1</td>
<td>Trachea, bronchus, lung cancers</td>
<td>5.6</td>
</tr>
<tr>
<td>4 Diarrheal diseases</td>
<td>6.7</td>
<td>Lower respiratory infections</td>
<td>4.7</td>
</tr>
<tr>
<td>5 Perinatal conditions</td>
<td>5.5</td>
<td>Chronic obstructive pulmonary disease</td>
<td>3.5</td>
</tr>
<tr>
<td>6 Measles</td>
<td>4.3</td>
<td>Colon and rectum cancers</td>
<td>3.2</td>
</tr>
<tr>
<td>7 Tuberculosis</td>
<td>3.6</td>
<td>Diabetes mellitus</td>
<td>2.3</td>
</tr>
<tr>
<td>8 Ischemic heart disease</td>
<td>3.1</td>
<td>Stomach cancer</td>
<td>2.0</td>
</tr>
<tr>
<td>9 Cerebrovascular disease</td>
<td>2.9</td>
<td>Breast cancer</td>
<td>2.0</td>
</tr>
<tr>
<td>10 Road traffic injuries</td>
<td>1.6</td>
<td>Alzheimer and other dementias</td>
<td>1.8</td>
</tr>
</tbody>
</table>

*Source: World Health Report, 2000*
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Approach
Collaboration & Partnership

- A capacity increase at all levels is urgent
- It is not necessary that there should exist as many national Pharmacopoeias as there are countries
  - Same true for pharmaceutical law & National agencies

- 5 non-ICH regions have started harmonization
  - APEC (Asia – Pacific Economic Cooperation)
  - ASEAN (Association of South East Asian Nations)
  - GCC (Gulf Cooperation Council)
  - PANDRH (Pan-American Network of Drug Regulatory Harmonization)
  - SADC (Southern African Development Cooperation)

Source: Participative Conference Health Security Agencies 2007: The global harmonization process in pharmaceuticals; J.L. Valverde
Approach
Regional Partnership

• Capacity limitations
  • Middle income
    • Model based on acceptance of foreign marketing licenses
    • Capacity to assess a generic drug file of national drug industry
    • Capacity to assess dossier of generic drug with origin in developing country
  • Insufficient capacity for data in a registration file for a new drug
    • Maker / importer of a drug to provide documentation of approval by a competent / internationally accepted authority
    • Alternative: product included in WHO prequalification list
    • Capacity to assess a generic drug file of national drug industry
    • Capacity to assess dossier of generic drug with origin in developing country
  • Countries with very limited financial & technical resources
    • Responsibility for import of essential drugs delegated to selected procurement agents
    • Generic marketing authorization for essential drugs based on published standard monograph in standard pharmacopeia

➢ Regional collaboration to increase capacity

Source: HNP Brief #4, April 2005
Approach  
International Partnership

- Role of WHO
  - Training, facilitation of information exchange
  - Expertise
  - Prequalification procedure

- Role of large drug regulatory agencies
  - Indirect support
    - Transferable priority review vouchers – FDA
    - Article 58; Scientific advice - EMEA
  - Direct support to DRA
    - Direct support - US offer to Pakistan (20th Aug 2008)
    - Support to specific R&D programs
    - Informal advice
    - Additional, extended meetings

➢ Partnerships welcome & encouraged!
Conclusions

ICDRA Recommendations 2006

- Proactive engagement of small DRAs in international cooperation at regional and global levels
- Adaptation of regulatory system to possibilities
  - Use of established regulatory pathways
  - Stepwise development of capacities
    ➢ Respect & expedite access to essential medicines
- Combat counterfeit and substandard drugs
  - Information sharing
  - Control of private market
- Implementation of pharmacovigilance
  - Focus on medicines approved under special conditions
  - International collaboration