Challenges to ensure the safety of products in a globalized world

A Product Development Partnership perspective

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Product Development Partnerships (PDPs)
NCEs, new vaccines, diagnostics on the clinical path

Vaccine
- hiv/aids
- tuberculosis
- malaria
- ntd
- diarrhea
- respiratory

Microbicides & preventatives
- dndi
- ivcc
- tba

Therapeutic product
- dndi
- medicines for malaria venture

Diagnostics
- cd4 initiative
- find

Source: Product Development Partnerships (PDPs)
Pipeline Begins to Be Filled
143 Candidates

104 biopharmaceutical candidates in development...

... and 39 diagnostic & vector control candidates

Notes: Includes products not funded by Gates Foundation. Biopharmaceutical candidates in development include: IAVI, IPM, IVI, GATB, Aeras, MMV, MVP, PVS, DNDi, iOWH, PDVI, HHVI. Source: PDPs

Slides source from: Bill & Melinda Gates Foundation & The Boston Consulting Group

Drugs Vaccines Microbicides

Pre Clinical 59 57%
Phase I 14%
Phase II 12%
Phase III 10%
Registration 2%
Launched 6%

0 2 4 6 8 # candidates

Diagnostics

Feasibility 7 26%
Test Development 7 26%
Evaluation 6 22%
Demonstration 1 4%
Country Adoption 6 22%

Vector control

Early Stage In Development 5 7

0 2 4 6 8 # candidates

CD4 FIND IDRI

IVCC
A changing research landscape for endemic NRAs

- Majority of treatments submitted for approval in «endemic» countries used to be ones already approved (EMA, FDA ...) or generic drugs
- New Chemical Entities, vaccines, combination treatments now being developed to respond to specific needs in developing countries
- Regulatory agencies with variable resources are facing new challenges
- Benefit risk assessment requires field understanding
**Our plan: 11 to 13 new treatments by 2018**

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<th>Discovery</th>
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<th>Clinical</th>
<th>Implementation</th>
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<td>Screening</td>
<td>Nitroimidazole backup (HAT)</td>
<td>Fexinidazole (HAT)</td>
<td>ASAQ Fixed-Dose Artesunate/ Amodiaquine</td>
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<td>Consolidated</td>
<td>Oxaborole backup (HAT)</td>
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<td>VL-2098 (VL)</td>
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<td>NECT (Stage 2 HAT) Nifurtimox - Eflornithine Co-administration</td>
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<td>Alternative formulations of Amphotericin B (VL)</td>
<td>New VL treatments – Africa • AmBisome® • Miltefosine</td>
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<td>Nitroimidazole backup (VL)</td>
<td>New VL treatments – (Latin America)</td>
<td>New VL treatments in Asia (SD AmBisome®, 3 drug combinations)</td>
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<td>Fenarimol series (Chagas)</td>
<td>HIV / VL</td>
<td>Benznidazole Paed. dosage form (Chagas)</td>
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<td>Flubendazole - Macrofilaricide (Helminth)</td>
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<td>Improved PI for 1st-line</td>
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<td>• Prodrugs of LPV/RTV</td>
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<td>• New formulations of LPV/r (Paed. HIV)</td>
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**Major Collaborators**
- Sources for hit and lead compounds: GSK, Anacor, Merck, Pfizer, Novartis (GNF, NITD), TB Alliance, ...
- Screening Resources: Eskitis, Institut Pasteur Korea, SCYNEXIS, Univ. Dundee, ...
- Reference screening centres: LSHTM, Swiss Tropical & Public Health Institute, University of Antwerp

**DNDi**

*Drugs for Neglected Diseases initiative*
Geographical distribution

Trans national
Trans regional
Trans continental  
but all neglected

Note: pins indicate regions of reported cases and are non proportional to endemicity
Utilizing and Strengthening Research Capacities in Disease-Endemic Countries

Major Role of Regional Disease Platforms:

- Defining patients’ needs and target product profile (TPP)
- Strengthening local capacities
- Conducting clinical trials (Phase II/III studies)
- Facilitating registration
- Accelerating implementation of new treatments (Phase IV & pharmacovigilance studies)
DNDI’s experience on regulatory challenges, before, during and after approval

Before

Variable, unpredictable timelines, sometimes duplicate reviews by ECs and NRAs for clinical trial approval

During

Format of dossier, nature of applicants, technical review, repeated site inspection, SPCs vary

After

Pharmacovigilance requests often unclear & infrastructure poorly resourced
Lack of process for geographical extension
Case study

- Product A produced & registered in India
- Added on the WHO-EML
- Submitted for approval in 4 countries in Africa (same dosage & indication)
  - File adaptation for each country
  - Agent/Applicant identification for each country
  - Parallel review in each country
- Country 1 approved product
- Countries 2, 3 and 4 expressed need to first conduct their own site inspection and then average 6 months review time

**Impact:** delays access
duplicates use of NRAs resources
Various models reaching to harmonisation & capacity strengthening

Drug

ASAQ (malaria)
ASMQ (malaria)
Fexinidazole (sleeping sickness)
Paromomycin for Visceral Leishmaniasis

Model

WHO PQ and joint WHO training
ASEAN
EMA-Art58/WHO and FDA joint Scientific Advice
Joint North/South/South Ethics workshop / pivotal clinical study
AMRH?
Pediatric dosage of benznidazole

ANVISA approval December 2011 - Next steps:
registration in other endemic countries
discuss path to access for smaller population in
EU/USA/Japan
Some bottlenecks …

- Confidentiality agreements
- Conflict of interest
- Standards

Pivotal role of WHO
In summary

- The success of PDPs to provide access to new medicines answering unmet medical needs, depends on sound technical evaluation of their benefit-risk.

- In a globalized world, the complexity of variable regulatory resources requires a flexibility of approach.

- The approach will rest on matching technical competencies from well-resourced NRAs with those of the endemic countries’ field experience on the disease & the healthcare system.

- Joint reviews are ways to encourage capacity strengthening but also to fast-track them and avoid duplication.
  - DNDi’s recent experience of WHO-PQ and EMA art-58/FDA were positive.
Thank you