Where Do We Stand with Drug Development for Neglected Diseases?

Lessons Learned from a Decade of R&D

Bernard Pécoul, Executive Director
Responding to the Needs of Patients Suffering from Neglected Diseases

- Malaria
- Leishmaniasis
- Paediatric HIV
- Sleeping Sickness (HAT)
- Chagas Disease
- Filaria
Landscape – What Has Changed Over the Past Decade
Global Burden of Communicable Diseases
A Little Better Is Not Good Enough for Africa

Global Burden 1990
- 69% Non communicable diseases
- 31% Communicable diseases

Global Burden 2010
- 77% Non communicable diseases
- 23% Communicable diseases

Sub-Saharan Africa 1990
- 45.2% Non communicable diseases
- 54.8% Communicable diseases

Sub-Saharan Africa 2010
- 50.3% Non communicable diseases
- 49.7% Communicable diseases
Sub-Saharan Africa Particularly Affected by NTDs

- Buruli Ulcer
- Chagas disease (American trypanosomiasis)
- Cysticercosis
- Dengue/Severe dengue
- Dracunculiasis (guinea-worm disease)
- Echinococcosis
- Fascioliasis
- Human African trypanosomiasis
- Leishmaniasis
- Leprosy
- Lymphatic filariasis
- Onchocerciasis
- Rabies
- Schistosomiasis
- Soil transmitted helminthiasis
- Trachoma
- Yaws
Fatal Imbalance Remains Despite Progress Over A Decade

- 3.8% of new products for neglected diseases (reformulations, combinations)
- 1.2% of NCEs for neglected diseases
- Only 1.4% clinical trials (of nearly 150,000 trials) focus on neglected diseases
- Only 1% of global health investment for neglected diseases*

756 products developed (excluding vaccines) (2000-2011)

- NCEs: 395
- Other products: 332
- Other diseases: 4
- Vaccines: 25


Source: Pedrique B et al, DNDi/MSF forthcoming publication, 2013
### ACCELERATING WORK TO OVERCOME THE GLOBAL IMPACT OF NEGLECTED TROPICAL DISEASES

**A ROADMAP FOR IMPLEMENTATION**

<table>
<thead>
<tr>
<th>Disease</th>
<th>2015</th>
<th>2020</th>
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<tbody>
<tr>
<td>Rabies*</td>
<td>Eradication</td>
<td>Global elimination</td>
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<tr>
<td></td>
<td></td>
<td>South-East Asia and</td>
</tr>
<tr>
<td>Blinding trachoma</td>
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<tr>
<td>Endemic trypanosomiasis (Gyraus)</td>
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<td></td>
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<tr>
<td>Leishmania</td>
<td></td>
<td></td>
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<tr>
<td>Chagas disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human African trypanosomiasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visceral leishmaniasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dracunculiasis</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Lymphatic filariosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Onchocerciasis</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Schistosomiasis</td>
<td>✓</td>
<td>✓</td>
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</tbody>
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**Sustaining the drive to overcome the global impact of neglected tropical diseases**

Second WHO report on neglected tropical diseases

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**Neglected tropical diseases**

The Executive Board,

Having considered the report on neglected tropical diseases,¹

RECOMMENDS to the Sixty-sixth World Health Assembly the adoption of the following resolution:
30 January 2012, London: ‘Uniting to Combat NTDs’

Global coalition to support WHO 2020 NTD Roadmap:

- Pharmaceutical industry leaders
- World Bank
- Donor countries (UK, USA, UAE)
- BMGF & other private donors (Mundo Sano, Brazil)
- Endemic country MoHs
- DNDi
Product Development Partnerships (PDPs): Filling Gaps in Translational Research and Product Development

PDPs work across different diseases and modalities

- **Vaccine**
  - avian
  - AERAS
  - mviPATH
  - PATH Dengue Vaccine Initiative
  - PATH Vaccine Development Program
  - Sabin Vaccine Institute
  - International Vaccine Institute

- **Microbicides & preventatives**

- **Therapeutic product**

- **Diagnostics**

- **DNDi**

- **HIV/AIDS**
- **TB**
- **Malaria**
- **NTD**
- **Diarrhea**
- **Respiratory**

Source: Product Development Partnerships (PDPs): Filling Gaps in Translational Research and Product Development
New Actors Dynamize The System
From Microscope to Bedside

**Fundamental Research**
- New science produced

**R&D**
- New pipelines

**Implementation**
- New implementation partners: Global Fund, GAVI, UNITAID, PEPFAR, etc.
DNDi: Who We Are, What We’ve Done Over the Past Decade
Patient Needs-Driven & Innovative R&D Model

- Deliver 11 to 13 new treatments by 2018
- Establish a robust pipeline
- Use and strengthen existing capacity in disease-endemic countries
- Raise awareness and advocate for increased public leadership

Founding Partners

- Indian Council for Medical Research (ICMR)
- Kenya Medical Research Institute (KEMRI)
- Malaysian MOH
- Oswaldo Cruz Foundation, Brazil
- Médecins Sans Frontières (MSF)
- Institut Pasteur France
- TDR (permanent observer)

7 worldwide offices
Disease Scope & Level of Investment
€ 400M for 2003-2018  => 11 to 13 Treatments

- **Discovery**
  - Leishmaniasis: € 100 M (5 treatments, 2 delivered)
  - HAT: € 50-60 M (1 treatment, 1 delivered)
  - Chagas: € 50-60 M (1 treatment, 1 delivered)
  - Filariasis: € 20-30 M (1 treatment)
  - Paediatric HIV: € 20-30 M (1 treatment)
- **Other NTDs**
  - Malaria > € 20 M (2 treatments, 2 delivered)
  - Other NTDs > € 10 M

Disease(s) to be chosen
Completed
DNDi Portfolio: Mix of Existing Drugs & NCEs
6 new treatments available and 12 new chemical entities in the pipeline

**Research**
- Screen
- Hit to Lead

**Translation**
- Pre-clinical
- Phase I
- Phase IIa/PoC

**Development**
- Phase IIb/III
- Registration
- Access

**Implementation**
- NECT
- SSG&PM
- New VL treatments
  - for Bangladesh
  - for Africa
  - for VL in India
  - for Latin America

**Malaria**
- ASAQ FDC
  - Artesunate-Amodiaquine Fixed-Dose Combination
- ASMQ FDC
  - Artesunate-Mefloquine Fixed-Dose Combination

**Paediatric HIV**
- New treatments

**Filaria**
- New treatments
- Benznidazole Paediatric Dosage form
- Flubendazole Macrofilaricide
- Biomarkers
- K777
- Azoles E1224
- Anfoleish (CL)

**Leishmaniasis**
- Nitroimidazole backup
- Oxaborole backup
- Nitroimidazole backup (VL)
- Fexinidazole (VL)
- Oxaborole SCYX-7158
- Fexinidazole

**HAT**
- Fenarimol series
- Nitroimidazole
- VL-2098
- Anfoleish (CL)

**Chagas**
- K777
- Nitroimidazole

**Paediatric**
- Two ‘4-in-1’ LPV/r-based Fixed-Dose Combinations
- RTV Superbooster for HIV/TB co-infection

**New Chemical Entity (NCE)**
- Fexinidazole (for HAT and VL) = 1 NCE
6 New Treatments Developed Since 2007

- ASAQ (Fixed-dose combination of artesunate + amodiaquine)
  - 2007
  - Malaria
- ASMQ (Fixed-dose combination of artesunate + mefloquine)
  - 2008
  - Malaria
- NECT (Nifurtimox-eflornithine combination therapy)
  - 2009
  - Sleeping sickness
- SSG&PM (Sodium stibogluconate & paromomycin combination therapy)
  - 2010
  - VL
- NEW VL TREATMENTS IN ASIA (SD AmBisome® / PM+M / A®+M /)
  - 2011
  - VL
- Benznidazole
  - 12.5 mg
  - Pediatric dosage form of benznidazole
  - Chagas disease

☑ Easy to Use ☑ Affordable ☑ Field-Adapted ☑ Non-Patented
Sleeping Sickness: From Unacceptable To Better, Towards Tools for Elimination

10 years ago:
Eflornithine
Mebendazole

Since 2009:
NECT

2016?
Oral treatment & rapid diagnostic test
10 Years Ago: A Dire Situation

<table>
<thead>
<tr>
<th>Melarsoprol</th>
<th>Eflornithine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxic (~5% mortality)</td>
<td>Expensive</td>
</tr>
<tr>
<td>Ineffective (resistance)</td>
<td>Difficult to use</td>
</tr>
<tr>
<td>Painful when delivered</td>
<td>Not registered in endemic regions</td>
</tr>
</tbody>
</table>
Since 2009, NECT: Improved Treatment But Still Not Ideal in Remote Areas

Nifurtimox-eflornithine combination therapy

- MSF & Epicentre initiated trial
- A simplified, safe & effective treatment for stage 2 HAT
- WHO Essential Medicines List (2009)
- Implemented in 12 Countries
- Drastic decrease in melarsoprol use

NECT Use (May 2013)

Treatments for stage 2 HAT in DRC (2012)
By 2016? New Oral Treatments and Rapid Diagnostic Tests at Village Level

**Fexinidazole**
- A ‘rediscovered’ new chemical entity through compound mining
- Potential oral treatment
- Phase II/III in DRC and CAR

**Oxaborole SCYX-7158**
- New chemical entity from the Lead Optimization programme
- Potential oral treatment with a single pill
- Phase I ongoing; Entering Phase II/III in 2014

**In partnership with Sanofi**
Visceral Leishmaniasis: From Toxic to Better Tolerated, Towards Oral Treatment for Africa

10 years ago:
SSG

Since 2010:
SSG&PM

Future:
Oral treatment
Treatment HIV/VL
Treatment PKDL
10 Years Ago: Unbearable Treatment Limitations for VL

- Toxic
- Painful when delivered
- Ineffective (resistance)
- Not registered in all endemic regions
Since 2010, SSG&PM: Improved Therapy for Africa, Yet Far From Optimal

SSG&PM
- Recommended by WHO in 2010 and National programmes
- Shorter-course treatment (17 days) but still injections
- PV study ongoing
- PM registered in Uganda and Kenya

Different efficacy of medicines by geographical areas

<table>
<thead>
<tr>
<th>Drugs</th>
<th>SSG</th>
<th>Ampho B Liposomal</th>
<th>Ampho B deoxycholate</th>
<th>MIL</th>
<th>PM sulphate</th>
<th>SSG+PM</th>
<th>LAB+SSG</th>
<th>LAB+MIL</th>
<th>PM+MIL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asia</td>
<td>35-95% (depending on areas)</td>
<td>&gt; 97% all regions</td>
<td>&gt; 97%; single dose: &gt; 96%</td>
<td>94-97% (India)</td>
<td>94% (India)</td>
<td>Not documented</td>
<td>&gt; 97%</td>
<td>&gt; 97%</td>
<td>&gt; 97%</td>
</tr>
<tr>
<td>Africa</td>
<td>93%</td>
<td>33 - &gt;97% (depending on areas)</td>
<td>Not fully established</td>
<td>72%</td>
<td>84%</td>
<td>91%</td>
<td>87%</td>
<td>79%</td>
<td>Not documented</td>
</tr>
</tbody>
</table>

Source: van Griensven, 2010
Future: Many Treatment Challenges Due to the Complexities of the Disease

- **Oral treatment**
  - Nitroimidazoles
    - Fexinidazole for VL
    - VL-2098
    - Other nitroimidazoles
  - Oxaboroles

- **HIV/VL co-infection**

- **Post Kala Azar Dermal Leishmaniasis**
Malaria: Develop ACTs in Fixed-dose Combos
Over 200 Million Treatments of ASAQ FDC Distributed

- Pre-qualified by WHO in 2008
- Non-patented product
- Registered in 30 sub-Saharan African countries, India, Bangladesh, Colombia
- Only ACT FDC with a 3-year shelf life
- Ambitious risk management plan (Pharmacovigilance) with MMV and Sanofi
- Transfer of technology to Zenufa (Tanzania)

Source: Sanofi

In partnership with Sanofi

Source: Sanofi
Paediatric HIV: New Field, Specific Mission
Treatment for Infants and Toddlers

- 4 products in 1: granules (FDC)
- Simply open and use with water, milk, food
- Palatable
- No cold chain
- Suitable for infants (< 2 mos-3 yrs)
- TB-treatment compatible
- Affordable

Modular format allows flexibility to replace drug in the combination

4-in-1 granules in Fixed-Dose Combinations

In partnership with Cipla

In partnership with Cipla
Filaria: Targeting the Most Neglected Specific Co-infection Contexts

- Develop a macrofilaricide to kill adult worms
- Focus on areas of co-infection with *Loa loa* and either onchocerciasis or lymphatic filariasis
What We Have Learned Over the Past Decade

- Patient Needs-Driven
- Scientific Challenges
- Partnerships
- Endemic Countries
- Access
- Sustainable Funding
Patient Needs-Driven: Beginning With The End In Mind

Definition of the Target Product Profiles with experts of endemic countries, researchers, clinicians, control programmes, patients associations, WHO, etc.

**TPP Criteria**
- Indications
- Population
- Clinical Efficacy
- Safety and Tolerability
- Stability
- Route of Administration
- Dosing Frequency
- Cost
Patient Needs-Driven
Simple, Adapted, Ready-to-Use

Fixed-dose ASAQ (w/ Sanofi)
Artesunate/amodiaquine
3 dosage strengths available

- Infants (4.5-8 kg)
  - AS: 25 mg
  - AQ: 67.5 mg

- Young Children (8-17 kg)
  - AS: 50 mg
  - AQ: 135 mg

- Children (17-35 kg)
  - AS: 100 mg
  - AQ: 270 mg

- Adults (≥36 kg)
  - AS: 100 mg
  - AQ: 270 mg

Co-blistered non-fixed AS+AQ
Artesunate-amodiaquine
AS: 50 mg; AQ 135 mg
Scientific Challenges
Boosting Innovation & Clinical Trials in Difficult Settings

- Accessing good quality compound libraries, knowledge, and data
- Consortia with public & private partners to create synergy and avoid duplication
- Open innovation models & knowledge sharing to reduce cost of development and ensure equitable access
- Clinical trial design to rapidly progress to proof-of-concept
- Innovative and tools/techniques adapted to the field
Partnerships: No One Can Do It Alone
A Global Network to Leverage Resources

Criteria for Success:

- Share the same vision
- Mutual understanding
- Involvement throughout the whole process
Endemic Country Engagement
Utilizing and Strengthening Research Capacities

Clinical Research Platforms
- Defining patient needs and TPP
- Strengthening local capacities
- Conducting clinical studies (Phase II/III)
- Facilitating registration
- Accelerating implementation of new treatments

Transfer of technology
- Data Management Centre – Nairobi
- Clinical sites with good practices
- Building networks of excellence (i.e. ANDi)
Endemic Country Engagement
Over 600 People Involved, Half in Africa

Annual plan DNDi, 2013
Access
Overcoming Regulatory Barriers

- Stronger regulatory reviews in Africa by national regulatory agencies (NRAs)
- New collaborations between RAs and ECs have shown to be fruitful
- Support to existing initiatives (EDCTP and African Medicines Regulatory Harmonization)
- WHO plays a pivotal role
Access
Ensuring Affordability of Treatments

- Price objective defined in license agreement (i.e. <1$ for ASAQ)
- Non-exclusivity: competition to drive price down
- Cost in TPP (i.e. nitros not expensive)
- Reduction of cost of API (i.e. mefloquine with MMV)

Example of ACTs price for malaria

Source: The Global Fund 2011
Sustainable Funding
Emergence of New Sources and Mechanisms

- New countries entering the field (BRICS, endemic countries)
- New funding mechanisms: UNITAID, Financial Transaction Tax
- New incentives: Milestone prize, etc.
Sustainable Funding
Diversification of Donors to Ensure Independence

**Private Donors**
- Médecins Sans Frontières (€48.2M)
- Bill & Melinda Gates Foundation (€43.5M)
- Wellcome Trust (€4.3M)
- Medicor Foundation (€2M)
- Other Private Foundations (incl. Slim, Starr, €2.8M)

**Public Donors**
- United Kingdom – DFID (€38.4M)
- Netherlands – DGIS (€17M)
- France – AFD & MAEE (€14.3M)
- UNITAID (€13.1M)
- Spain – AECID (€12M)
- Switzerland – SDC & Geneva (€11.8M)
- Germany – KFW & GTZ (€9M)
- European Union – FP5,6,7 & EDCTP (€4.4M)
- USA – NIH/NIAID (€1.8M)
- The Global Fund – AMFm (€0.5M)
- Brazil – MoH (€0.4M)
Challenges for The Next Decade
Contribute to Control or Elimination of Neglected Diseases

Reaching the 2020 WHO NTD Goals

- **Diseases Targeted For Elimination**: Guinea worm, Leprosy, Lymphatic filariasis, Blinding trachoma, Sleeping sickness

- **Diseases Targeted For Control**: Schistosomiasis, River blindness, Soil-Transmitted Helminthes, Chagas, Visceral Leishmaniasis

- Where we are now, Where we can get with existing tools and strategies, Where we can get with new tools and strategies

2020 Goals
Global Framework for R&D for Neglected Diseases

- Coordination of efforts
- Leadership from endemic countries
- Central role of WHO
- WHA Resolution
Keep Patients at the Core of Our Mission

Give a voice to neglected patients.

They exist, they must be heard.

Yvette, HAT patient, Bandundu-Ville, DRC, 2012