FDA-NIH EFFORT TO CAPTURE THE GLOBAL CLINICAL EXPERIENCE OF DRUG REPURPOSING TO FACILITATE DEVELOPMENT OF NEW TREATMENTS FOR NEGLECTED INFECTIOUS DISEASES (INCLUDING NEGLECTED TROPICAL DISEASES AND EMERGING THREATS)

NEEDS AND OPPORTUNITIES
The concept of Neglected Diseases:
A R&D gap

- Poorest of the poor
- Living in remote areas
- Socioeconomic burden on family and community
- Marginalized & voiceless patients
Many Neglected Diseases at various control stages

<table>
<thead>
<tr>
<th>WHO NTDs</th>
<th>Diarrheal diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>List of 17</strong></td>
<td>Amebiasis, Giardiasis, Cryptosporidium, Cholera, Shigella, E. coli enterotoxigenic,</td>
</tr>
<tr>
<td>Buruli ulcer, Chagas disease</td>
<td>E. coli enteriaggregative enteropathogenic, Campylobacter, Non-typhoidal</td>
</tr>
<tr>
<td>Cysticercosis/taeniasis</td>
<td>Salmonella enterica, Typhoid and paratyphoid fever, Rotavirus</td>
</tr>
<tr>
<td>Dengue, Dracunculiasis, Echinococcosis,</td>
<td></td>
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<tr>
<td>Fascioliasis, Human African</td>
<td></td>
</tr>
<tr>
<td>trypanosomiasis, Leishmaniasis, Leprosy,</td>
<td></td>
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<tr>
<td>Lymphatic filariasis, Onchocerciasis, Rabies,</td>
<td></td>
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<tr>
<td>Schistosomiasis, Soil-transmitted helminthiasis</td>
<td></td>
</tr>
<tr>
<td>Trachoma</td>
<td></td>
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<tr>
<td>Yaws</td>
<td></td>
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<tr>
<td><strong>Other neglected conditions</strong></td>
<td></td>
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<tr>
<td>Mycetoma, snake bite, scabies, chronic</td>
<td></td>
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<tr>
<td>suppurative otitis media, podoconiosis</td>
<td></td>
</tr>
</tbody>
</table>

**The «big 3»**

TB, HIV malaria
Approved products (2000-2011)
A deficit persists for neglected and infectious diseases

NCEs and New Products Deficit Analysis

Deviation from expectation in percent

Source: The drug and vaccine landscape for neglected diseases (2000—11): a systematic assessment; Dr Belen Pedrique et al; the Lancet 2013. Deficit analysis was not part of the published version.
25 (67%) of recently approved products for NDs consisted in New Formulations, New Indications or FDC.
<table>
<thead>
<tr>
<th>Indication (Disease)</th>
<th>Products</th>
<th>Galenic form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leishmaniasis</td>
<td>Paromomycin (LV)</td>
<td>Inj. 375mg/ml</td>
</tr>
<tr>
<td></td>
<td>Miltefosine (LV)</td>
<td>Capsule 10mg&amp;50mg</td>
</tr>
<tr>
<td></td>
<td>Miltefosine (Additional Indication=Cutaneous L)</td>
<td>Capsule 10mg&amp;50mg</td>
</tr>
<tr>
<td>Human African trypanosomiasis</td>
<td>Nifurtimox-Eflornithine Combination Therapy (NECT)</td>
<td>Nifurtimox new indication in association</td>
</tr>
<tr>
<td>Leprosy</td>
<td>Thalidomid</td>
<td>Tablets</td>
</tr>
<tr>
<td>Acute Diarrhoea</td>
<td>Zinc sulfate</td>
<td>oral liquid, in 10 mg per unit dosage forms; tablet, in 10mg per unit dosage form</td>
</tr>
<tr>
<td>Cholera</td>
<td>Tosufloxacin tosilate hydrate</td>
<td>Fine Granules 15% for Pediatric (Ozex)</td>
</tr>
<tr>
<td>TB</td>
<td>Moxifloxacin (as hydrochloride)</td>
<td>Tablets 400mg</td>
</tr>
<tr>
<td></td>
<td>Levofloxacin</td>
<td>Tablets 250mg and 500 mg</td>
</tr>
<tr>
<td></td>
<td>Ofloxacin</td>
<td>Tablets 200mg and 400 mg</td>
</tr>
<tr>
<td></td>
<td>Atovaquone&amp;Proguanil</td>
<td>Tablets adults and paediatric tablets for &gt; 11 kg</td>
</tr>
<tr>
<td></td>
<td>Atovaquone&amp;Proguanil</td>
<td>film-coated tablets. (Malarone® Enfants) 5-11kg 2003 FDA</td>
</tr>
</tbody>
</table>

10 (27%) of recently approved products for NDs consisted in New Indications (including pediatric one) combining:
- Extension of anti-infectives
- New indication
Neglected Diseases: Treatment Limitations 10 Years Ago

- Ineffective (resistance)
- Toxic
- Expensive
- Painful when delivered
- Difficult to use
- Not registered in endemic regions
- Restricted by patents

We Need Safe, Effective, Easy-to-Use Drugs
DNDi Portfolio-Building Model:
Address Immediate Patient Needs & Deliver Innovative Medicines

Long-term projects

• New chemical entities (NCEs)

Medium-term projects

• New formulations (fixed-dose combinations)
  • New indications of existing drugs

Short-term projects

• Completing registration dossier
  • Geographical extension

- Discovery
  - R
  - LS
  - LO
- Pre-clinical
- Clinical
- Implementation
Advantages of repurposing drugs at the clinical stage

Saving time to patients by
- De-risking (safety)
- Increasing chances of success
- Saving costs

Phase 1 showing the need to administer tid to prevent digestive side effects and maximum dose of 150mg/day (planned for oncology)

- 1986: development of a model to infect macrophages with leishmanial donovani (Croft)
- 1987: Alkyl phospholipids identified as possible candidates (Croft et al.)
- 1990s: Initially developed in several cancer indications with insufficient efficacy in phase II trials
- 1992: cure in mice with L donovani and L infantum (Kuhlencord et al)

Developed by ASTA Medica- Zentaris later Paladin – who applied for NDA in 2013 and was granted the PRV –
- No new phase 1 – additional PK data derived from CTs in Leishmanaisis patients
Generic drug development timelines for VL
A significant time gain for repurposed drugs

Minimum 2 years saved
The process of repurposing … example 1: HAT
A pragmatic and opportunistic scientific approach

- 1922: suramin
- 1941: pentamidine
- 1949: melarsoprol (effective but toxic)
- mid-1970s: nifurtimox (registered for Chagas disease)
- 1981: eflornithine (developed for cancer – nor efficacy but promising in reducing hair growth - developed as a topical cream for hirsutism) – shown effective in HAT- registered in 1990 for HAT and cream for hirsutism in 2000
- 2002: study in Uganda with MSF on 3 combinations
- 2009: Epicentre, and DNDi test nifurtimox-eflornithine combination in a non inferiority trial against eflornithine – NECT added to the WHO essential list and 1st line treatment
- 2009: fexinidazole, rediscovered after datamining of 700 nitroimidazole compounds, now in development in Man for stage 2 HAT
The process of repurposing … example 2
A pragmatic and opportunistic scientific approach

**Mycetoma**

A very neglected condition with a single possible low hanging fruit treatment approach

- chronic infection of failure results in poor treatment outcome
- existing treatment options are limited

**Clinical data for eumycetoma treatment**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient count</td>
<td>50</td>
</tr>
<tr>
<td>Response rate</td>
<td>80%</td>
</tr>
<tr>
<td>Adverse events</td>
<td>5%</td>
</tr>
</tbody>
</table>

**Madurella mycetomatis highly susceptible to ravuconazole**

**Fos ravuconazole dose rationale**

- Modeling of plasma concentrations against Madurella mycetomatis

**Study design: «drop the loser»**

- Interim analysis
- Surgical removal of encapsulated lesion

Dosing: fos ravuconazole 200 mg on Day 1, 2, and 3 and weekly thereafter
But are there any risks?

- **Scientifically**: … if data from the repurposed compound are not solid … (but this can be evaluated) – especially regarding the safety documentation

- **Regulatory**: … acceptability of the NDA dossier will depend on the stage from “repurposing”
  - Different for a licensed drug vs non licensed vs licensed since a long time

- **For the Industry**: emergence of new safety signals (e.g due to different population)

- **For the patient and public health system**: affordability and sustainable production
In conclusion …

The gap for safe and effective treatments for NDs or Neglected patients exist!
Accessing clinical candidates is an opportunity to shortcut the R&D process and accelerate therefore access to needed treatments
Anticipation of regulatory needs and access plan are crucial

Repurposing has already shown its benefit for NTDs, and should be encouraged