DNDi needs for future registration of new treatments in Africa

Els Torreele – Manica Balasegaram
DNDi project managers

Best Science for the Most Neglected

Type of products/treatments in the DNDi pipeline

- Geographical extension of indication of an already elsewhere registered drug
- Drug combinations
  - Fixed dose combinations
  - Co-administration schedules
  - Components registered as monotherapy or not
- New formulations of existing drugs
  - E.g. paediatric formulations
- New chemical entities (NCEs)

DNDi

Best Science for the Most Neglected

The case of human African trypanosomiasis (HAT)

- Only endemic in sub-Saharan Africa;
  - Low number of cases (~10,000 reported; 50 – 70,000 estimated)
  - few cases elsewhere (sporadically travellers)
- No market at all; few drugs available
- Limited knowledge on the disease – little experience in conducting clinical trials
  - Major logistic and capacity constraints
  - Access to patients (remote, scattered, insecurity)
- Clinical development methodology not well established
  - Diagnosis and staging, Test of Cure, surrogate markers, …

Best Science for the Most Neglected

NECT: nifurtimox-eflornithine combination therapy

- Eflornithine: registered for HAT (USA, France)
- Nifurtimox: registered in several Latin-American countries for Chagas disease
  - Some data on compassionate use in HAT, but insufficient to support registration (+ only poor efficacy in monotherapy)
- MSF-Epicentre-DNDi: Clinical trial to demonstrate the efficacy and safety of a co-administration of nifurtimox-eflornithine for stage 2 HAT
  - No-one in support of a strategy to jointly register (by Bayer & s-a) this combination; unclear whether technically feasible
- Chosen strategy - succesful:
  1. include in WHO's EML based on clinical data
  2. Countries to approve for use, e.g CAR, DRC, others to follow

Best Science for the Most Neglected

Fexinidazole: a first NCE for HAT

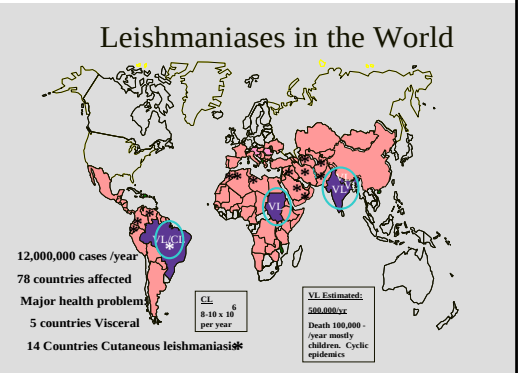
- *Objective:* timely registration of safe, effective and quality drug in endemic countries and access to patients
  - How to assist endemic countries to do so?
- Different options to be explored (or combination of):
  - First filing through:
    - FDA
    - EMEA art 58 (includes WHO)
    - Other European country: France, Switzerland,…

    Only if endemic country input can be integrated in process?
  - Orphan Drugs Status (protocol assistance, financial support)
  - Direct registration in endemic countries
    - With input from regulatory experts, e.g from FDA, EMEA, other
  - Methodology to be developed (expert WG) and validated by regulators, incl FDA, EMEA, endemic country regulators?
- HOW to choose? ease, relevance, time, cost – who decides?

Best Science for the Most Neglected

The case of visceral leishmaniasis (VL)

- South Asia, East Africa, Brazil.
- PM & Miltefosine developed and registered in India; L-AMB also registered
- Not the case for e.g. East Africa
- Combinations recommended



1. There urgent need for geographic extension of currently available drugs to other key endemic countries
2. Urgent need for combinations that can address disease spectrum
3. Harmonization of trials methods needed, but may need different approaches in different countries/ regions

Best Science for the Most Neglected

Paramomycin in Africa

- Treatment registered in India after large phase III trial, also now in EML. Currently being evaluated in combination with L-Amb by DNDi.
- DNDi started a phase III trial in 2004. Initial dosage of 15mg/kg for 21d not efficacious in Sudan; dose increased now to 20mg/kg for 21 d.
- Regional approach: Aim is to register drug with local regulatory authorities after completion of 0104 trial in Kenya, Sudan, Ethiopia and Uganda.
- Local partners key in this process: engagement with regulatory authorities through LEAP
- Next step is to have country recommendations through national guidelines: engagement with MoH control programs in LEAP