Pharmaceutical development of drugs for neglected tropical diseases

Dr Stephen Robinson
DND*i*, Geneva

APS PharmSci 2016
Glasgow, 5 September

Best science for the most neglected

Presentation outline:

- The fatal imbalance: a brief history of DND*i*
- Collaborating for success: our Product Development Partnership model
- Special challenges in the NTD space
- Best science for the most neglected – opportunities for pharmaceutical innovation

A brief history of DND*i*

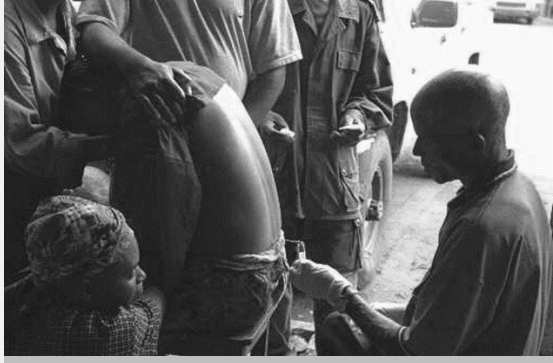
Origins of DND*i*

1999

- First meeting to describe the lack of R&D for neglected diseases
- MSF commits the Nobel Peace Prize money to the DND Working Group
- JAMA article: *'Access to essential drugs in poor countries - A Lost Battle?'*

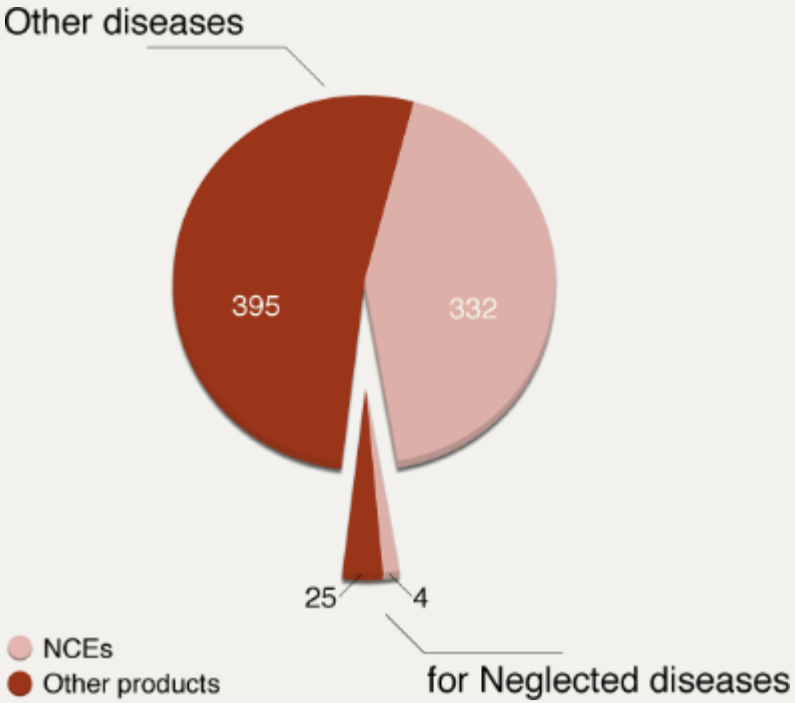
July 2003

- Creation of DND*i*
- Founding partners:
    - *Institut Pasteur, France*
    - *Indian Council of Medical Research, India*
    - *Kenya Medical Research Institute, Kenya*
    - *Médecins Sans Frontières*
    - *Ministry of Health, Malaysia*
    - *Oswaldo Cruz Foundation/Fiocruz, Brazil*
    - *WHO –TDR (Special Programme for Research and Training in Tropical Diseases) as a permanent observer*



Fatal imbalance still exists, an adapted R&D response is required

756 products developed (excluding vaccines & biologicals) (2000-2011)*



* Source: Pedrique B et al. The drug and vaccine landscape for neglected diseases (2000-11): a systematic assessment. *Lancet Global Health*, Early Online Publication, 24 Oct 2013.

DND*i*'s Mission

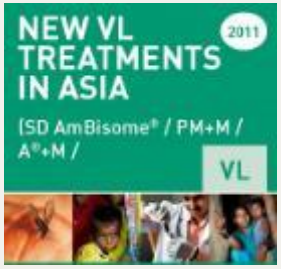
- To develop new drugs or new formulations of existing drugs for **people suffering from neglected diseases**.
- To develop drugs for the **most neglected diseases** (such as sleeping sickness, leishmaniasis, and Chagas disease), while considering engagement in **R&D projects for other neglected patients** (e.g. malaria, paediatric HIV, filarial infections)
- To **strengthen capacities in a sustainable manner**, including through know-how and technology transfers in the field of drug R&D for neglected diseases.
- To adopt **a dynamic portfolio approach**

DND*i*'s PRIORITY:

Neglected Patients

…from bench to bedside

7 new treatments delivered, recommended, implemented



- ✓ Easy to use
- ✓ Affordable
- ✓ Field-adapted
- ✓ Non-patented

- **30 projects, 8 diseases areas**
- **13 entirely new chemical entities (NCEs)**
- **Over 160 partnerships,** most in endemic countries
- **160 staff**, half in endemic countries & 700 people working on DNDi projects
- **EUR 400 million** raised equally from public and private sources
- **4 regional disease-specific clinical trial platforms/ networks** and several technology transfers

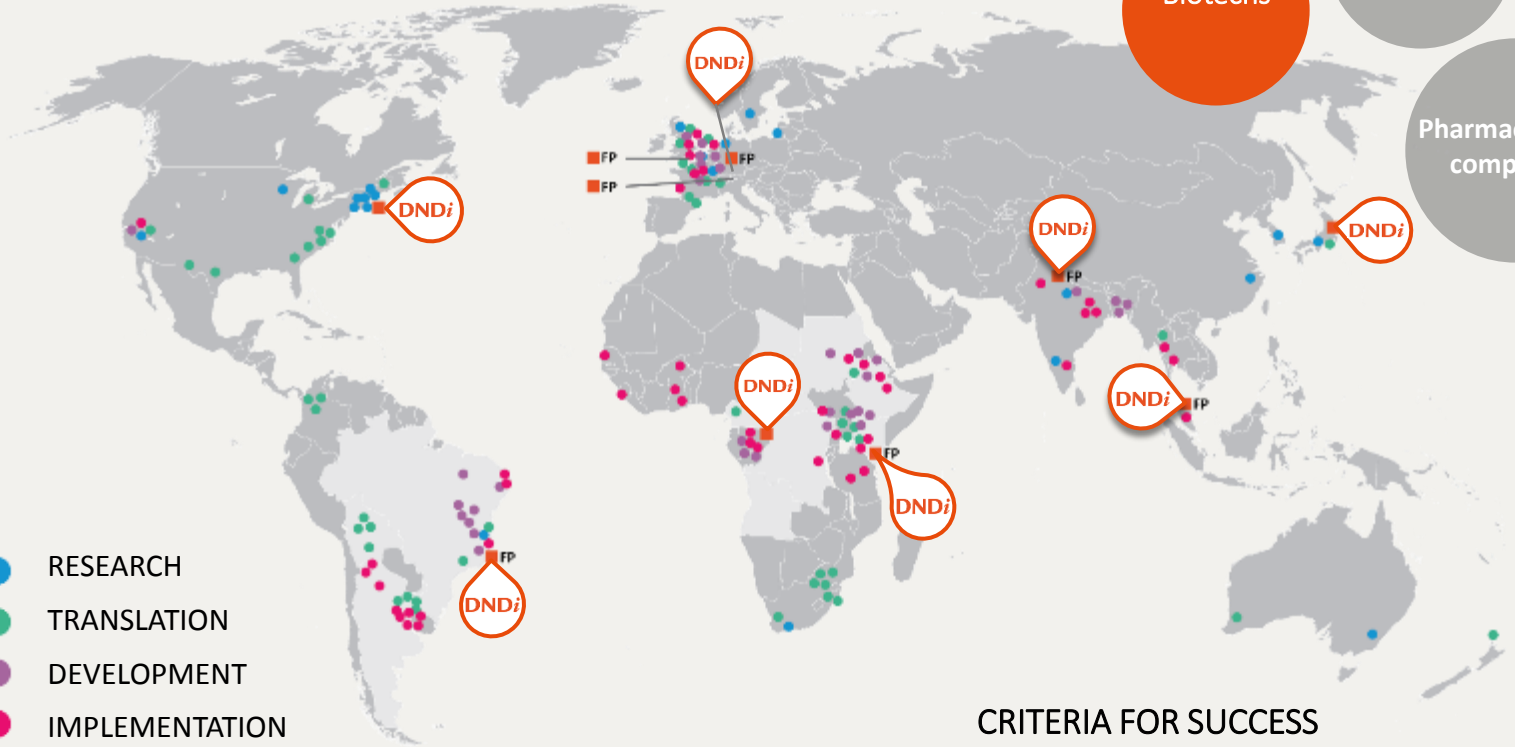
DND*i* Product Development Partnership Model

Some key features of the DND*i* PDP model

- At the core: leveraging a global network of institutional, pharma and CRO partners
- Regional disease platforms
- Diversified funding (public:private)
- Patient focused:
  - Target Product Profiles (TPP)
  - Affordability and sustainability
    - Medicines as public goods – licensing and IP strategies
    - Decoupling of R&D costs from pricing
- Dynamic portfolio model and range of support models

DND*i*'s success is only possible through innovative partnerships

Over 160 partnerships worldwide



- RESEARCH
- TRANSLATION
- DEVELOPMENT
- IMPLEMENTATION

- PLATFORM MEMBER COUNTRIES
- DNDi WORLDWIDE
- FP FOUNDING PARTNERS

PDPs

Biotechs

Int. Org. & NGOs

Universities & Research Institutes

Pharmaceutical companies

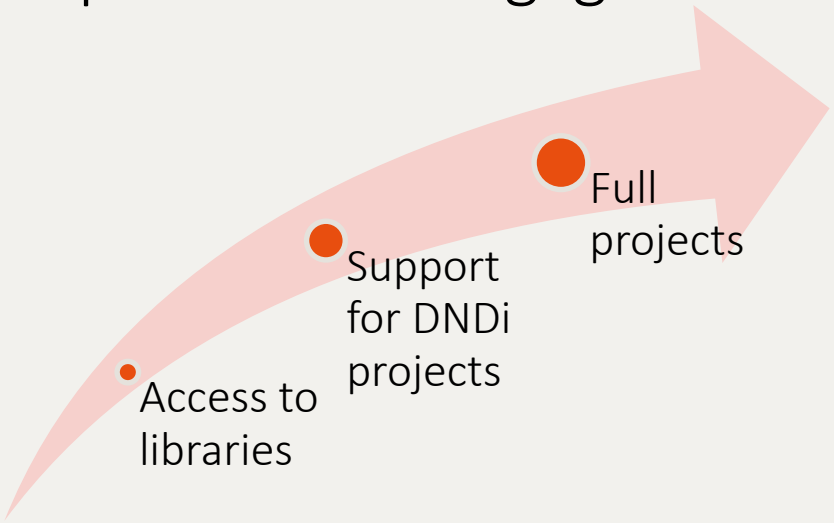
CROs

CRITERIA FOR SUCCESS

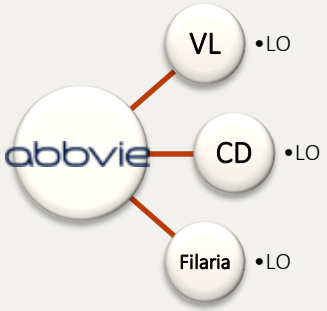
- ✓ Share the same vision
- ✓ Mutual understanding
- ✓ Involvement throughout the whole process

Some of DND*i*'s pharma and biotech partnerships

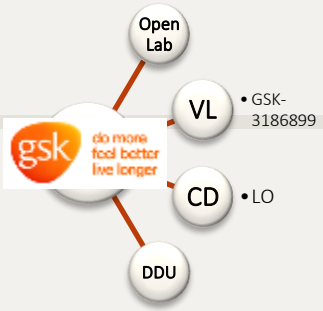
- Productive Discovery partnerships
  - Fully collaborative discovery projects
  - Access to compound libraries
  - Support for DND*i* projects
- A spectrum of engagement



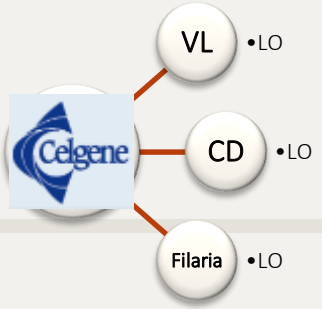
Dedicated NTD group & support for DNDi projects



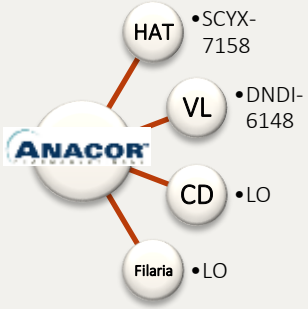
Dedicated DDW DPU & Open Lab



Dedicated Global Health Group



Boron chemistry platform & Dedicated NTD group



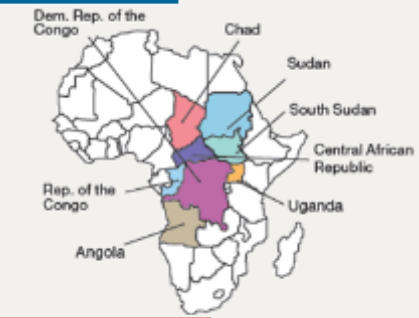
VL = visceral leishmaniasis, CL = cutaneous leishmaniasis, CD = Chagas disease, LO = lead optimisation

Partnering and research capacity building with MoHs and national control programmes

VL

LEAP
LEISHMANIASIS
EAST AFRICA PLATFORM

HAT



CHAGAS

Major Role of Regional Disease Platforms:

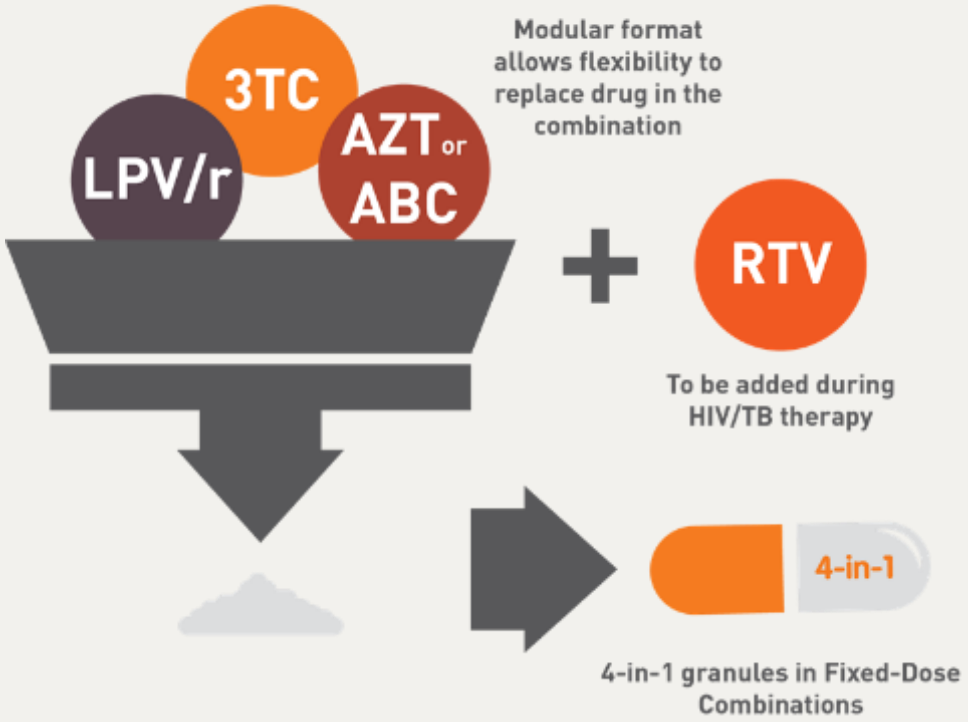
- Strengthening local capacities
- Conducting clinical trials (Phase II/III studies)
- Facilitating registration
- Accelerating implementation of new treatments (Phase IV & pharmacovigilance studies)
- **Defining patients' needs and target product profile (TPP)**

For each disease, a Target Product Profile to guide all decisions (paediatric HIV example)

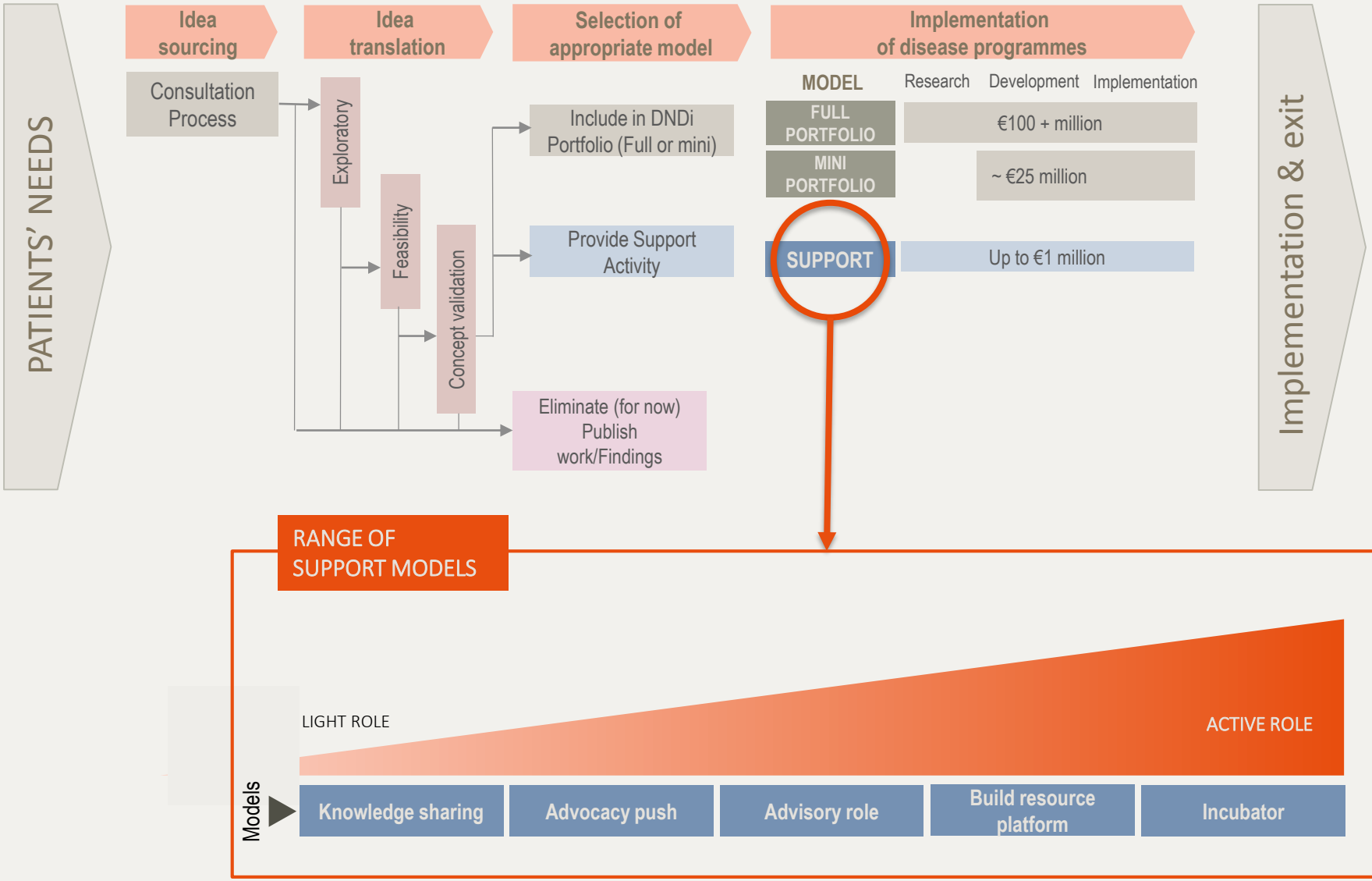
IDEAL CHARACTERISTICS (TPP)

- 4 ARVs in one
- Simple to open and use with water, milk, food
- Good taste
- No fridge needed
- Suitable for infants (<2 months - 3 years)
- TB-treatment compatible
- Affordable for governments

PROCESS



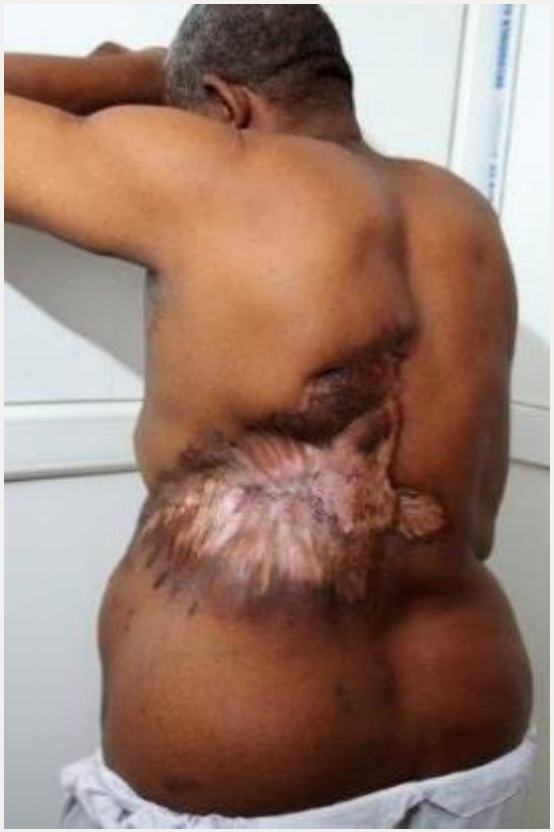
Dynamic portfolio and support models



Dynamic portfolio: new disease areas, new models…

Neglected diseases

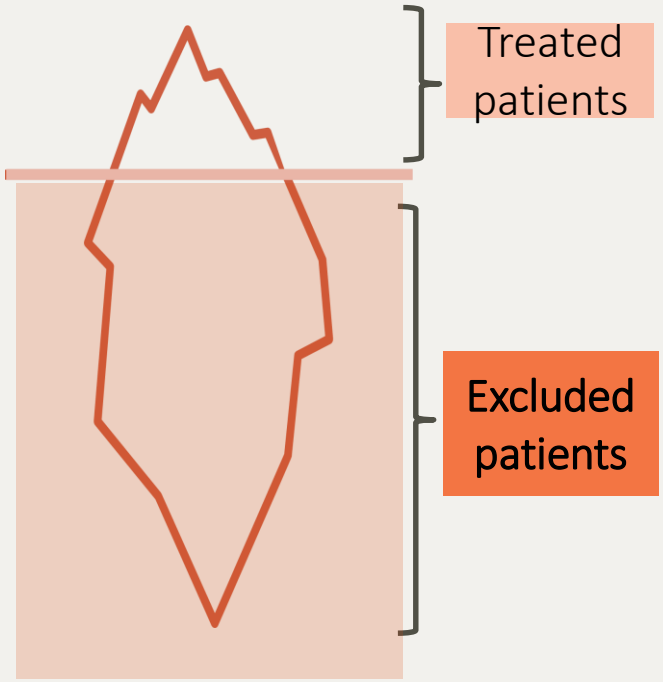
Mycetoma



Testing fosravuconazole

Neglected patients

Hepatitis C



Public health approach

Neglected models

Antimicrobial resistance

Incubation of GARD

A pan-genotypic treatment for less than $300

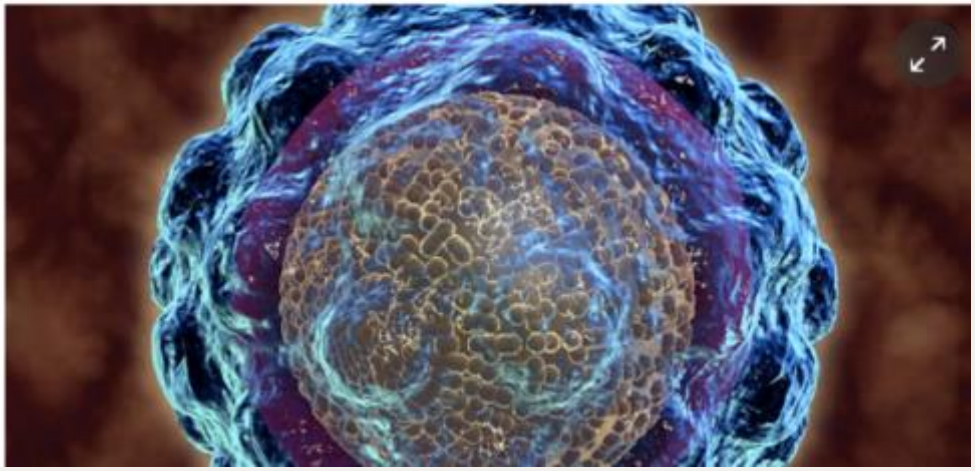
- DND*i*, Pharco and Presidio agreement to test combination of sofosbuvir + ravidasvir
- Partnership with Malaysia and Thailand to conduct Phase II/III multicentre study (900 patients)
- Using innovative licensing agreement or TRIPS flexibilities

theguardian

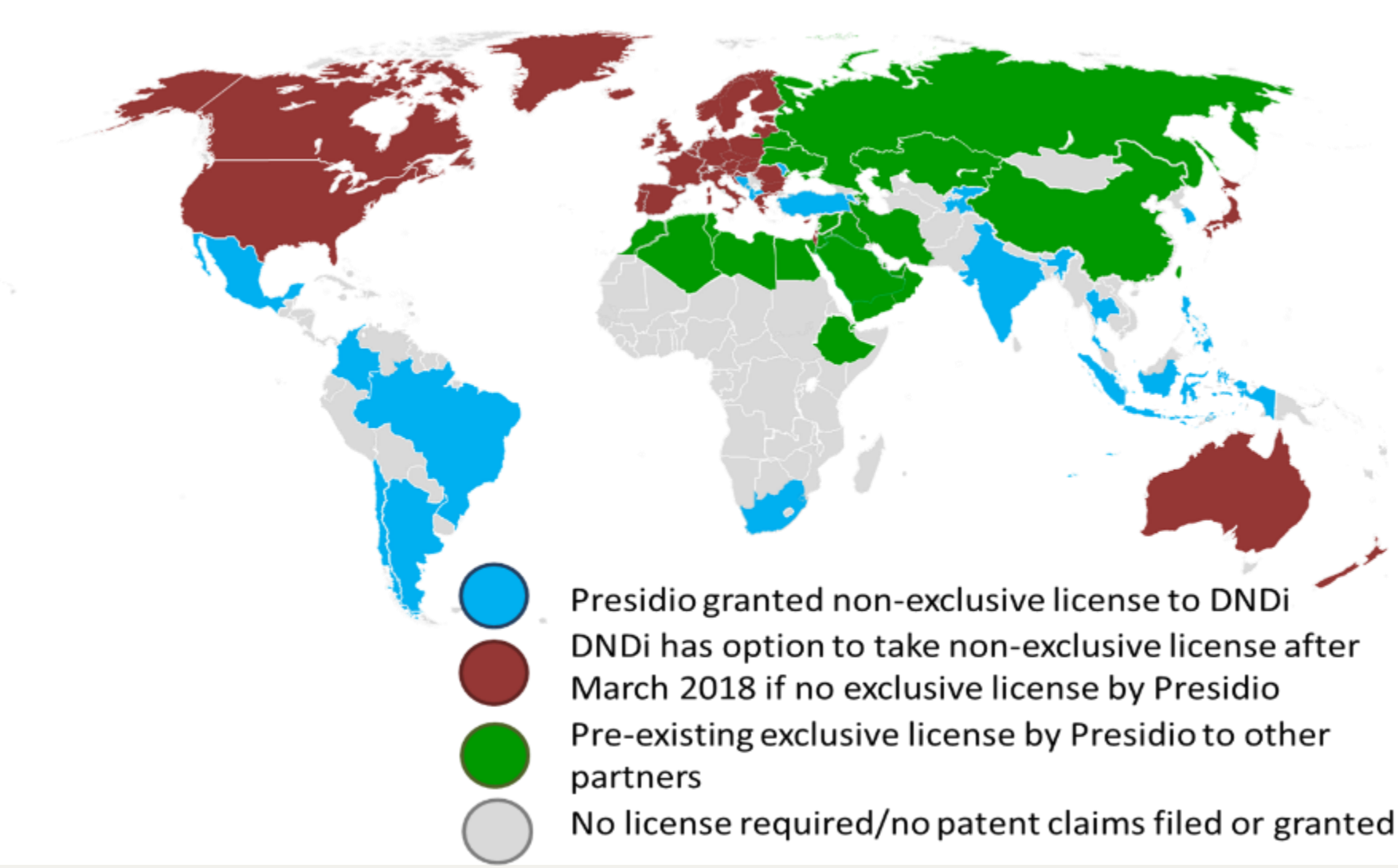
April 13, 2016

Hepatitis C treatment for under $300 coming soon

Drugs for Neglected Diseases initiative says drug successfully tested in Egypt could be available within 18-24 months



An innovative licensing agreement for ravidasvir that covers a very large territory



Special challenges in the NTD space

Pharmaceutical development at DND*i*

- Virtual model - all development and manufacturing outsourced
  - NCEs and commercial products used as IMPs
  - CDMO or industrial partner holds manufacturing licenses
- Trend away from vertically integrated CDMOs:
  - Companies focusing on core competences, e.g. manufacture, packaging, parenterals
  - DNDi has to manage multiple hand-offs in IMP supply chain
- Risk aversion:
  - Pushing wide acceptance limits citing lack of experience
  - Limiting liabilities in case of batch failure

Key pharmaceutical development challenges

Technology selection:

- Low solubility chemical space and frequently high dose
- Stability in climatic zone IVb
- Affordable and sustainable cost of treatment
- Agnostic to eventual industrial partner capabilities

Regulatory:

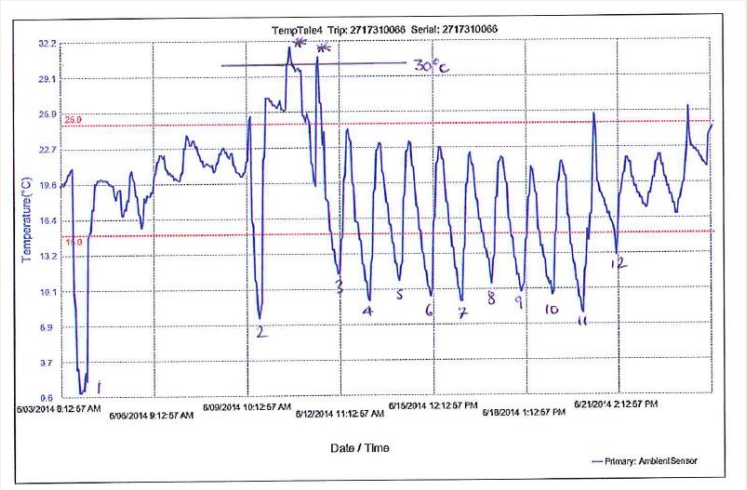
- Regional co-operation and harmonisation
- Requirements minimal to extensive
- Agency capacity and experience

Other economic and social factors:

- Education and training
- Supply chain security and falsified medicines
- Company outlook (public vs. private, domestic → multinational → global)
- Minimal approach to pharmaceutical development

Focus on reproducibility rather than robustness → technology transfer issues

Product distribution and storage



Opportunities for pharmaceutical innovation

Address immediate patient needs & deliver innovative medicines: short- and long-term

New chemical entities (NCEs)

New formulations

New indications for existing drugs

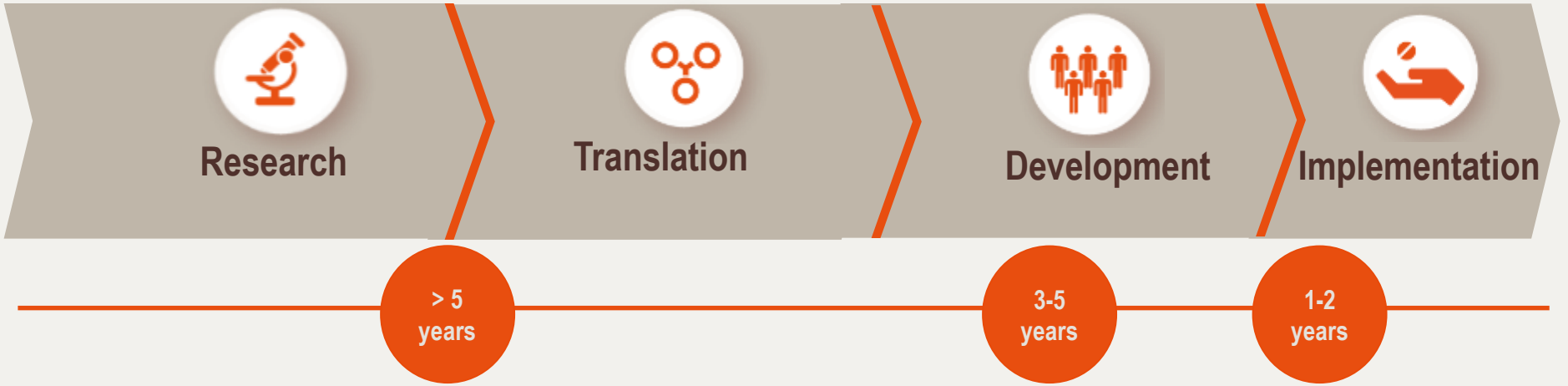
Completing registration dossier

Geographical extension

Long-term projects

Medium-term projects

Short-term projects

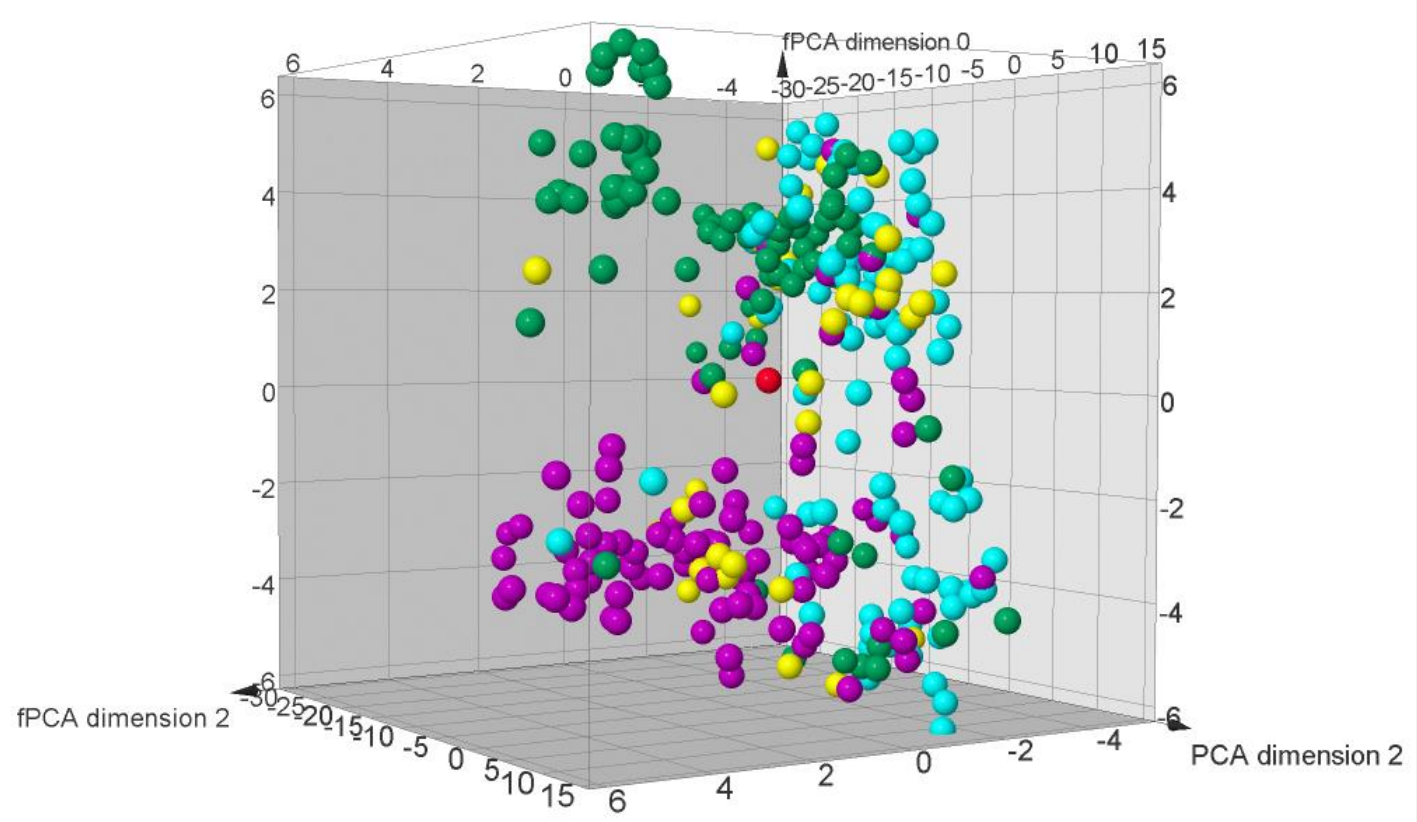


NTD Drug Discovery Booster

- The goal is faster, cheaper drug discovery for NTDs
- Rapid expansion of new screening hits through cross-collaboration with several Pharma

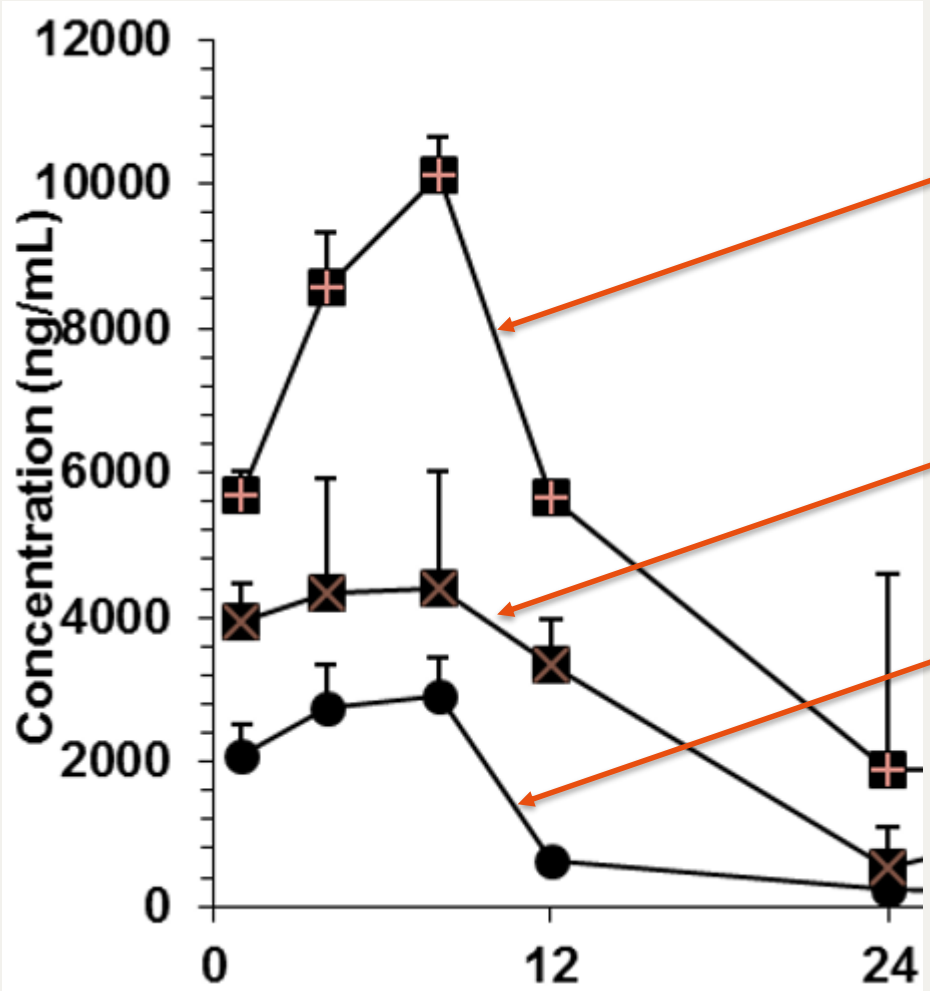
- DNDi generate additional SAR **before** commencing time consuming and expensive chemistry to make new analogues

Representative example



- Good coverage of chemical space by the Consortium screening process
- Clear distinct regions of coverage coming from individual consortium members

Enabling formulations – Visceral Leishmaniasis candidate

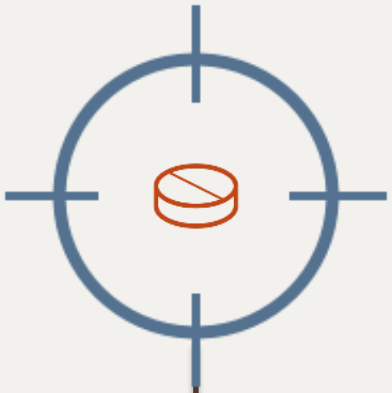


Nanomilled free base (d_{90} < 500 nm)

Micronised HCl salt

Free base

Sleeping sickness: two new treatments in development to support sustainable elimination



13 years ago

Melarsoprol:

Toxic, resistant

Eflornithine:

Not available

Since 2009

NECT

Improved therapy

2018?

Fexinidazole

Oral treatment (10 days)

Future objective

SCYX-7158

Single-dose, oral treatment

DNDi
Drugs for Neglected Diseases *initiative*

SCYX-7158 tablet quality risk assessment

Risk Matrix	Ingredient Attributes						
Drug Product CQA	API Polymorph	API PSD/ habit	MCC	DCP	SSG	PVP	MgSt
Appearance		1	2	2			
Weight Uniformity							
Water Content							
Assay		1					
Degradation products							
Dissolution	4	5	6	6	7	7	8
Microbial limits		3	3	3	3	3	3
Hardness		1	6	6			8
Friability		1	6	6			

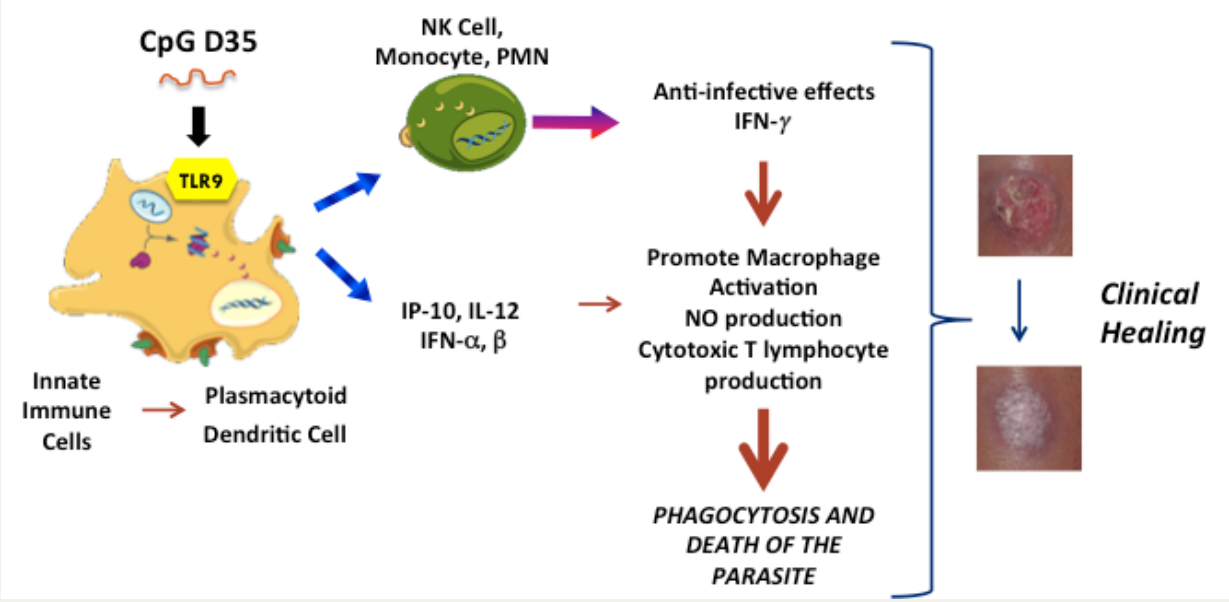
Table 8. **Risk matrix for P473 Process attributes (the numbers in the table link to the individual risks in the FMEA tables)**

Risk Matrix	Process Attributes							
Drug Product CQA	Granulation water (g)	Granulation speed (rpm)	Granulation time (min)	Gran spray (g/min)	Drying	Milling	Lubrication	Compression
Appearance	9, 10	9, 10	9, 10	9, 10	14	16	18	20
Weight Uniformity	10	10	10	10		16	18	21
Water Content								
Assay	11	11, 13	11, 13	11				21, 22
Degradation products	12	12	12	12	15			
Dissolution					14		17	19
Microbial limits								
Hardness	9	9	9	9	14		17	19,21
Friability								20

Integrated Cutaneous Leishmaniasis strategy: CpG D35

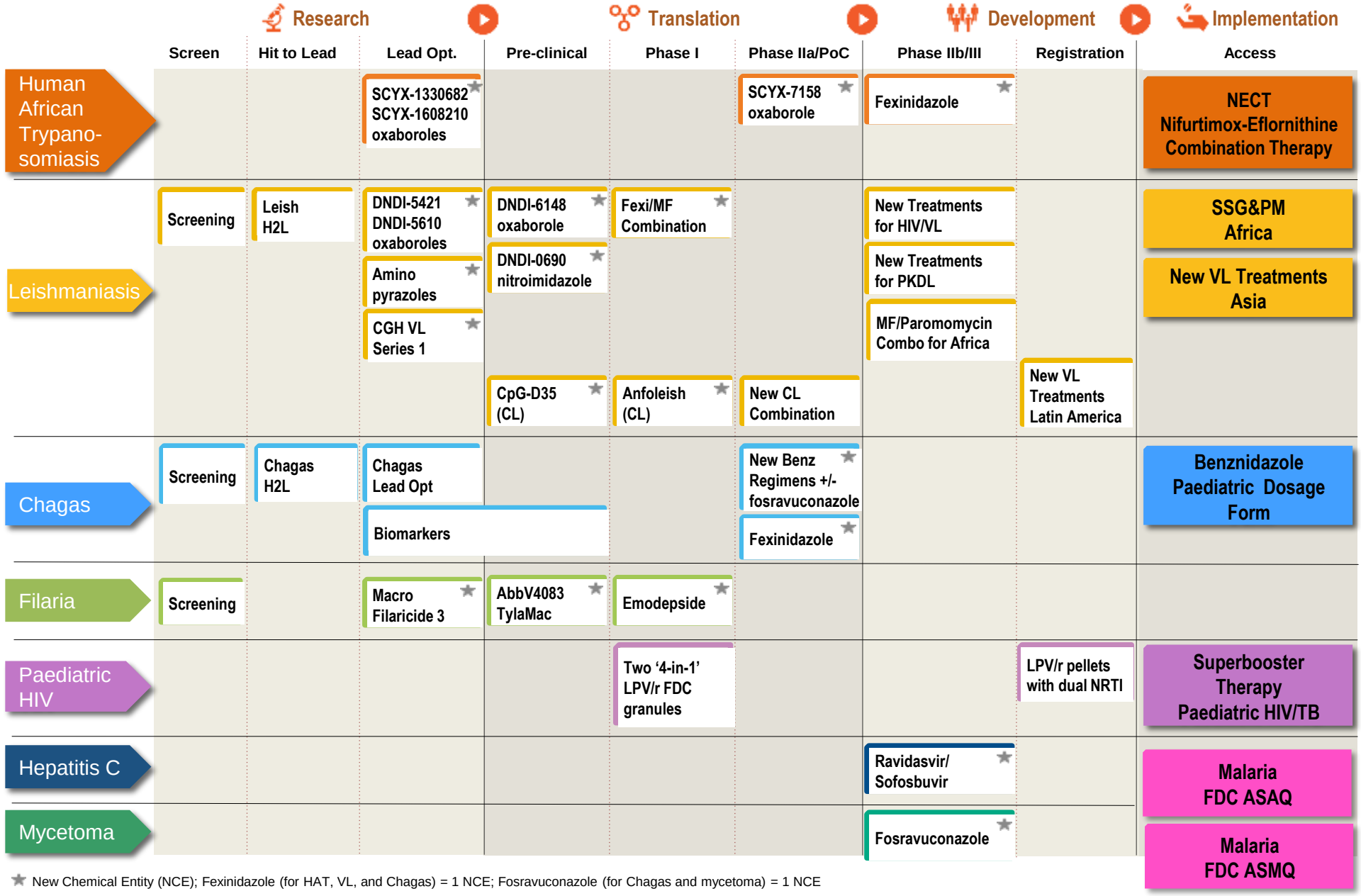
Disease presentation	Estimated incidence	Therapeutic modalities
Special forms (e.g. recidivans, diffuse, non-responsive, PKDL)	10-15%	CpG D35 + antiparastic drug
Multiple, large lesions, joints, face, ears	25-30%	Oral, systemic drug (multiple – lead optimisation)
1-4 lesions, ≤ 3 cm	60-70%	Topical (Anfoleish – Phase 1b/2)

CpG D35 stimulates the innate immune system:



DNDi R&D Portfolio June 2016

7 new treatments available and 15 new chemical entities in the pipeline



★ New Chemical Entity (NCE); Fexinidazole (for HAT, VL, and Chagas) = 1 NCE; Fosravuconazole (for Chagas and mycetoma) = 1 NCE

Summary and final remarks

Summary and final remarks

- DND*i* has built an innovative Product Development Partnership model which has delivered seven new treatments to date
- We have implemented a virtual R&D model effectively with a diversity of institutional and pharma partners
- Robust product design and development are critical to acheiving our mission for patients in the regions of the world where DND*i* operates
- Please connect with us to advance new treatments for NTDs:

www.dndi.org

THANK YOU

TO ALL OUR

PARTNERS & DONORS

DNDi
Drugs for Neglected Diseases *initiative*

MEDECINS SANS FRONTIERES

BILL & MELINDA GATES foundation

UKaid
from the British people

Ministry of Foreign Affairs of the Netherlands

afd
AGENCE FRANÇAISE DE DÉVELOPPEMENT

UNITAID

Federal Ministry of Education and Research
by KFW

Liberté • Égalité • Fraternité
RÉPUBLIQUE FRANÇAISE
MINISTÈRE DES AFFAIRES ÉTRANGÈRES

aecid
Agencia Española de Cooperación Internacional para el Desarrollo

EDCTP

GHIT Fund
Global Health Innovative Technology Fund

Schweizerische Eidgenossenschaft
Confédération suisse
Confederazione Svizzera
Confederaziun svizra

wellcome trust

NATIONAL INSTITUTES OF HEALTH

Ministério da Ciência, Tecnologia e Inovação
BRASIL

USAID
FROM THE AMERICAN PEOPLE

Norad

TDR

giz
Deutsche Gesellschaft für Internationale Zusammenarbeit (GIZ) GmbH

Fundación BBVA

UBS
UBS Optimus Foundation

The Global Fund
To Fight AIDS, Tuberculosis and Malaria

Regione Toscana

REPUBLIQUE ET CANTON DE GENEVE

Rockefeller Foundation
Innovation for the Next 100 Years

BNDES

ruta n
MEDELLÍN

SANDOZ-FONDATION DE FAMILLE

INSTITUTO Carlos Slim DE LA SALUD

medicor foundation

THE SASAKAWA PEACE FOUNDATION

THE STARR FOUNDATION


Give neglected patients a voice.
They exist and must be heard.
Thank you for your attention.
DNDi
Drugs for Neglected Diseases initiative