Pharmaceutical development of drugs for neglected tropical diseases

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DNDi, Geneva

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Best science for the most neglected
Presentation outline:

- The fatal imbalance: a brief history of DNDi
- 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 DNDi
Origins of DNDi

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 DNDi
- 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)*

DNDi’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**
DNDi’s PRIORITY: Neglected Patients

...from bench to bedside
7 new treatments delivered, recommended, implemented

- 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

✓ Easy to use
✓ Affordable
✓ Field-adapted
✓ Non-patented
DNDi Product Development Partnership Model
Some key features of the DNDi 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
DNDi’s success is only possible through innovative partnerships

Over 160 partnerships worldwide

CRITERIA FOR SUCCESS
✓ Share the same vision
✓ Mutual understanding
✓ Involvement throughout the whole process
Some of DNDi’s pharma and biotech partnerships

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

VL = visceral leishmaniasis, CL = cutaneous leishmaniasis, CD = Chagas disease, LO = lead optimisation
Partnering and research capacity building with MoHs and national control programmes

**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
Dynamic portfolio and support models

Idea sourcing
- Consultation Process

Idea translation
- Exploratory
- Feasibility
- Concept validation

Selection of appropriate model
- Include in DNDi Portfolio (Full or mini)
- Provide Support Activity
- Eliminate (for now)
  - Publish work/Findings

Implementation of disease programmes
- FULL PORTFOLIO
  - Research
  - Development
  - Implementation
  - €100 + million
- MINI PORTFOLIO
  - Up to €1 million

SUPPORT

RANGE OF SUPPORT MODELS

LIGHT ROLE
- Knowledge sharing
- Advocacy push
- Advisory role

ACTIVE ROLE
- Build resource platform
- Incubator

DNDi
Drugs for Neglected Diseases initiative
Dynamic portfolio: new disease areas, new models...

Neglected diseases
- Mycetoma
- Hepatitis C

Neglected patients
- Treated patients
- Excluded patients

Neglected models
- Antimicrobial resistance

Testing fosravuconazole

Public health approach

Incubation of GARD
A pan-genotypic treatment for less than $300

- DNDi, 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
An innovative licensing agreement for ravidasvir that covers a very large territory
Special challenges in the NTD space
Pharmaceutical development at DNDi

- 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)

Long-term projects

New formulations
New indications for existing drugs

Medium-term projects

Completing registration dossier
Geographical extension

Short-term projects

Research

Translation

Development

Implementation

> 5 years

3-5 years

1-2 years
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
SCYX-7158 tablet quality risk assessment

<table>
<thead>
<tr>
<th>Risk Matrix</th>
<th>Ingredient Attributes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug Product CQA</td>
<td>API Polymorph</td>
</tr>
<tr>
<td>Appearance</td>
<td>1</td>
</tr>
<tr>
<td>Weight Uniformity</td>
<td>1</td>
</tr>
<tr>
<td>Water Content</td>
<td>1</td>
</tr>
<tr>
<td>Assay</td>
<td>1</td>
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<tr>
<td>Degradation products</td>
<td>4</td>
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Dissolution

Microbial limits

Hardness

Friability

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

<table>
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<tr>
<th>Risk Matrix</th>
<th>Process Attributes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug Product CQA</td>
<td>Granulation water (g)</td>
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<tr>
<td>Appearance</td>
<td>9</td>
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<tr>
<td>Weight Uniformity</td>
<td>10</td>
</tr>
<tr>
<td>Water Content</td>
<td>11</td>
</tr>
<tr>
<td>Assay</td>
<td>11</td>
</tr>
<tr>
<td>Degradation products</td>
<td>12</td>
</tr>
<tr>
<td>Dissolution</td>
<td>14</td>
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DNDi
Drugs for Neglected Diseases Initiative
### Integrated Cutaneous Leishmaniasis strategy: CpG D35

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

**CpG D35 stimulates the innate immune system:**

- **CpG D35** interacts with TLR9 on immune cells.
- Activates innate immune cells (e.g., NK cells, monocytes, PMNs).
- Promotes macrophage activation and NO production.
- Induces IFN-γ and other cytokines (e.g., IL-12, IP-10).
- Enhances phagocytosis and death of the parasite.
DNDi R&D Portfolio June 2016
7 new treatments available and 15 new chemical entities in the pipeline

- **Human African Trypanosomiasis**
  - Screening: Leish H2L
  - Lead Opt: DNDI-5421, DNDI-5610 oxaboroles
  - Pre-clinical: DNDI-6148 oxaborole
  - Phase I: Fexi/MF Combination
  - Phase Ib/IIc: New Treatments for HIV/VL
  - Phase IIb/III: New Treatments for PKDL
  - Registration: MF/Paromomycin Combo for Africa
  - Access: NECT
  - Nifurtimox-Eflornithine Combination Therapy

- **Leishmaniasis**
  - Screening: Chagas H2L
  - Lead Opt: Amino pyrazoles
  - Pre-clinical: CGH VL Series 1
  - Translation: Cpg-D35 (CL)
  - Development: Anfoleish (CL)
  - Implementation: New VL Treatments Latin America

- **Chagas**
  - Screening: Chagas Lead Opt
  - Translation: New Benz Regimens +/- fosravuconazole
  - Implementation: Fexinidazole

- **Filaria**
  - Screening: Macro Filaricde 3 TylaMac Emodepside
  - Development: Two ‘4-in-1’ LPV/r FDC granules
  - Implementation: LPV/r pellets with dual NRTI

- **Paediatric HIV**
  - Screening: Amino pyrazoles
  - Development: AbbV4083
  - Implementation: Superbooster Therapy Paediatric HIV/TB

- **Hepatitis C**
  - Screening: Ravidasvir/Sofosbuvir
  - Implementation: Malaria FDC ASAQ

- **Mycetoma**
  - Screening: SCYX-1330682, SCYX-1608210 oxaboroles
  - Development: Fexinidazole
  - Implementation: Malaria FDC ASMQ

🌟 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

- DNDi 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 achieving our mission for patients in the regions of the world where DNDi operates
- Please connect with us to advance new treatments for NTDs: www.dndi.org
THANK YOU
TO ALL OUR
PARTNERS &
DONORS
Give neglected patients a voice. They exist and must be heard. Thank you for your attention.