Outline

- Neglected Tropical Diseases
- Products, Manufacturing, Supply Chain
- Regulatory Processes
- Organizations
- Examples
  - Soil Transmitted Helminth Infections
  - Schistosomiasis
  - Learning from others
- Q&A
Neglected Tropical Disease (NTD)

Neglected tropical diseases (NTDs) – a diverse group of communicable diseases that prevail in tropical and subtropical conditions in 149 countries – affect more than one billion people and cost developing economies billions of dollars every year. Populations living in poverty, without adequate sanitation and in close contact with infectious vectors and domestic animals and livestock are those worst affected.  

www.who.int/neglected_diseases

Buruli ulcer  
Chagas disease  
Dengue and Chikungunya  
Dracunculiasis (guinea-worm disease)  
Echinococcosis  
Foodborne trematodiases  
Human African trypanosomiasis (sleeping sickness)  
Leishmaniasis  
Leprosy (Hansen's disease)  
Lymphatic filariasis

Mycetoma, chromoblastomycosis and other deep mycoses  
Onchocerciasis (river blindness)  
Rabies  
Scabies and other ectoparasites  
Schistosomiasis  
Soil-transmitted helminthiases  
Snakebite envenoming  
Taeniasis/Cysticercosis  
Trachoma  
Yaws (Endemic treponematoses)
Neglected tropical diseases are a diverse group of tropical infections which are common in low-income populations in developing regions of Africa, Asia, and the Americas. They are caused by a variety of pathogens such as viruses, bacteria, protozoa and helminths.

These diseases are contrasted with the big three infectious diseases [malaria, HIV/AIDS, tuberculosis] which generally receive greater treatment and research funding. In sub-Saharan Africa, the effect of these diseases as a group is comparable to malaria and tuberculosis. NTD co-infection can also make HIV/AIDS and tuberculosis more deadly.


www.cdc.gov/globalhealth/ntd
NTD Factsheet
Type of Products

**Small Molecules**

**New Molecular Entities**

*Worldwide Development*
1) Adult -> Pediatrics
2) Pediatrics = primary indication

Included in development for US/EU markets
Stringent Regulatory Authorities, Regulated with PIPs, PSPs

*Regional/local approach*

**Patented**

**Off-Patent**

**Biologics/ Biosimilars**

**New Formulation**
Better, age-appropriate formulation

Generic market (Rx or OTC)

**Vaccines**

**WHO list of Essential Medicines**

Schaufelberger Consulting LLC

IQ PWG Webinar 20 Nov 2019
General Requirements

The “usual challenges”: acceptability, palatability, excipients

Plus:
- Stability (temperature & humidity); shelf life
- Large patient populations -> huge volume forecasts
- Suitable packaging for long, fragmented supply chain
- Simple instructions for administration, dosing
- Mindful of costs -> access
- Environmental impact (high volumes)
- Consider culture, health literacy, other initiatives e.g. education, sanitation

“Guidelines for Medicine Donations” 2010 by WHO & 11 other organizations, Third edition 2011
(www.who.int)
Dosage Forms

- Trend towards **ORAL SOLIDS**
  - Dispersible oral dosage forms
  - Granules (Sprinkle)
  - Minitablets
- **Suppositories**, e.g. artesunate 100 mg, WHO prequalified, malaria
- **Thin Films**
- **Microneedles**
- Avoid dosing devices?

Gerrard et al. (2019) “Innovations in Pediatric Drug Formulations and Administration Technologies for Low Resource Settings”

Dosing devices – **color coding**
Weight bands → color zones
=> Reduce dosing errors
**Epinephrine** injection i.m.
WHO List Essential Medicines

www.certadose.com
Trend in Dosage Forms: Minitables

Minitablet (1-3 mm)
Advantages:
- coating (taste masking)
- dispersible (-> NG tube)
- dose flexibility

Workshops 2019:
- MCERSI/IQ Consortium, Baltimore MD
- 11th Annual EuPFI Congress, Malmoe, Sweden

Trend/Publications:
- Suitable for younger age groups; neonates (?)
- Klingmann et al. (Prof. J. Breitkreutz)
- Strickley 2019 – review article oral solids
Manufacturing

Development/Clinical Supplies

- Liquids -> Solids
- Excipients: generally accepted and available
- Handling, administration: test concepts

Commercial/Donation Products

- Large volumes
- Scale-up, batch size
- Reduce costs
- Local manufacturing?

Fluid bed powder granulator/coater
ref: www.glatt.com
Protect Your Supply Chain!

10-30% of medicines sold in developing countries are counterfeit.

20-90% of antimalarial drugs failed quality testing (7 African countries)


Anticounterfeiting measures (over/covert)

API
Bulk Product
Packaged Product
Serialization
Rapidly Changing Environment

Temie Giwa-Tubosun, CEO Lifebank Nigeria; Africa Netpreneur Prize 2019 (Jack Ma)
www.netpreneur.africa  www.lifebank.ng
LinkedIn, Twitter, CNN

WeRobotics: non-profit organization, local training through “flying labs”
“….inclusion of local experts who know how to apply these [drone] technologies effectively and sustainably”  www.werobotics.org
Regulatory Processes

- EU/US HA submissions
  - Mandatory, incentives ("stick & carrot")
  - Incentives for NTDs
- National HA submissions
- Regional Harmonization?
  - African regions
  - CARICOM (Caribbean)
  - SEARN (South-East Asia)
- Other Processes:
  - WHO prequalification process
  - WHO collaborative (registration) procedure; sharing of assessment, inspection reports
  - Compendia, International Pharmacopoeia
WHO Prequalification aims to ensure that diagnostics, medicines, vaccines and immunization-related equipment and devices for high burden diseases meet global standards of quality, safety and efficacy, in order to optimize use of health resources and improve health outcomes.

www.who.int/topics/prequalification
WHO Prequalification (PQ)

Process:
- Expression of Interest (EOI) List
- Pre-submission meeting
- Dossier Review
  - Screening
  - Assessment
- GMP inspections
- Qualification
- Post-qualification variations

- **Scope**: only for certain therapeutic areas, limited to WHO priority medicines; medicines are already in WHO Model List Essential Medicines and/or WHO treatment guidelines;

- **Pathways**:
  - **Multisource generic products**: full review of dossier and inspection of sites by WHO PQT
  - **Innovator products and generics approved by stringent health authority (SRA)**
  - Others, e.g. EMA Article 58 – “EU Medicines for All” – EC No 726/2004

- **Quality standards for products worldwide**
  - Supply chain and distribution in climatic zone IVb
  - Stability testing
  - API testing at DP manufacturing site

- **Dossier** follow CTD structure but PQ template for summary modules

- **Impact**: procurement processes!

- Training offered by WHO
Organizations

- **UN**: WHO (Better medicines for Children resolutions 2007), UNICEF
- **National Health Authorities**
- **Philanthropic organizations**, e.g.
  - Bill Gates Foundation/Research Inst.
  - Clinton Health Access Initiative
  - Wellcome Trust
- **Public-Private Partnerships (PPPs)**, e.g.
  - Children Without Worms
  - Drugs for Neglected Disease initiative (DNDi)
  - GHIT (Japan)
  - Schistosomiasis Alliance
  - Tuberculosis Alliance

- **Academia**, Tropical Institutes
- **(Global) Public Health organizations**
- **Patient organizations**
- **Pharmaceutical Companies**
  - Research based
  - Generics
- **Pediatric focused**:
  - IQ Consortium, Pediatric Working Group
  - European Paediatric Formulation Initiative (EuPFI)
  - Indian Paediatric Formulation Initiative

*Multiple organizations for POLICY, FUNDING, DEVELOPING & MANUFACTURING, DISTRIBUTION/DONATION*
Assessments/Rankings

Access to Medicine Foundation

Access to Medicine Index

www.Accessstomedicinesfoundation.org

Source: Access to Medicine Index 2018

Communicable Diseases
Neglected Tropical Diseases
Maternal & Neonatal Health Conditions

IQ PWG Webinar 20 Nov 2019
Soil Transmitted Helminth (STH) Infections

- Intestinal worms: hookworms, roundworms, whipworms
- High disease burden: 1.5 to 2 billion people affected worldwide (850 million children)
- Economic/epidemiologic studies (Michael Kremer, Harvard, Nobel Prize Economics 2019)
- Preventive Chemotherapy (PC) or Mass Drug Administration (MDA); WHO recommends MDA if > 20% local STH prevalence; Review by Majid et al (2019)
- Donations: mostly albendazole and mebendazole; future need for NMEs
VERMOX® Chewable (mebendazole) 500 mg

- Extend age-range down to one year (London Declaration NTDs)
- Administration
  - Chew or place on spoon/water -> rapidly disintegrating
  - Formulation: 500 mg active, sweetener (sucralose) and flavor (strawberry)
- Clinical study *(Silber et al. 2017)*
- Regulatory pathway: US FDA approval; WHO prequalification (2019)
- API testing at FPP manufacturer; polymorph specs for FPP
- Partnering: Shaanxi Hanjiang Pharmaceutical (API) and Recipharm (formerly Lusomedicamenta) for finished pharmaceutical product (FPP)
- Donation program: replace tablet with chewable tablet; committed to 1 billion doses 2021-25  *Janssen/J&J press release April 29, 2019*
Schistosomiasis

- Bilharzia
- Blood flukes (trematode worms), Schistosoma species
- Freshwater snail (host)
- 78 countries (mainly in sub-Saharan Africa)
- >220 million require treatment (WHO 2017)
- Disease leading to chronic inflammation of the organs that can be fatal
- Disease causing anemia, stunted growth and impaired learning ability with devastating consequences for the lives of the very young children
- Mass Drug Administration (MDA)
- Clean water, sanitation and hygiene

Ref: DPRC Hospital & Diagnostic Lab, Dhaka    www.dprcbd.com

Ref: www.si.edu
Pediatric Praziquantel Consortium started pivotal Phase III study in Kenya

“The availability of a pediatric medication is essential to address the medical need of infected preschool-age children. Our investment today will secure our future generation”

Dr. Maurice Odiere, PI, Kenya Medical Research Institute (KEMRI)

"Limited access to medical services is a challenge for developing countries facing poverty. We wish to address it together through this new collaboration“

Dr. Jutta Reinhard-Rupp, Head of the Global Health Institute, Merck

• Merck KGaA (Germany)
• Astellas Pharma Inc. (Japan)
• Swiss Tropical & Public Health Institute (Switzerland)
• Lygature (The Netherlands)
• Farmanguinhos (Brazil)
• Schistosomiasis Control Initiative (UK)
• Kenya Medical Research Institute (Kenya)
• Université Félix Houphouët-Boigny (Cote D'Ivoire).

www.pediatricpraziquantelconsortium.com
Praziquantel Pediatric

Current:
600 mg Tablet for school age children + older

New (TPP):
• Small, orally dispersible tablet
• Take with or without water
• Acceptable taste
• Stable under Zone IVb conditions
• Suitable for 3 month to 6-year old children
• Intended for individual case treatment and mass treatment campaigns

Development:
• Racemic API -> L-PZQ only, lower dose, reduce bitter taste
• D-PZQ = inactive, bitter taste
• Clinical program Ph I-III
• Product availability target 2022

Ref: www.pediatricpraziquantelconsortium.com
Global Schistosomiasis Alliance

Mission: Eliminating schistosomiasis as a public health problem in partnership

“Schistosomiasis has a hugely detrimental effect on a child’s mental and physical development. By treating children we are giving them the opportunity to reach their full potential and live healthier, happier lives”

Ref: Global Schistosomiasis Alliance (GSA) - www.eliminateschisto.org
Learning from “The Big Three”

• “Big Three” = HIV/AIDS, Malaria, Tuberculosis
• Worldwide focus; not restricted to Low- and Middle-Income Countries (LMIC)
• Various funding models; public-private partnerships
• Philanthropic organizations starting drug discovery & development

• CMC: the same challenges -> Learnings
Learning from HIV/AIDS

Multiple Challenges Pediatric Dosage Forms
- Tablet size (!); fixed-dose combinations 2-4 actives!
- Ratio of active ingredients may differ across age groups
- “4-in-1”: abacavir/lamivudine/lopinavir/ritonavir, taste-masked granules, sprinkle capsule children < 3 years (DNDi, Cipla Ltd)

Toolkit for Research and Development of Paediatric Antiretroviral Drugs and Formulations
WHO and UNITAID in collaboration with IMPAACT (International Maternal Pediatric Adolescent AIDS Clinical Trials) network, PENTA (Paediatric European Network for Treatment of AIDS) foundation and experts from the Paediatric Antiretroviral Working Group – Module 5 on “Acceptability” - 2018

https://apps.who.int/iris/bitstream/handle/10665/273151/9789241514361-eng.pdf?ua=1
HIV – Switch Oral to LA Injectable

• Rilpivirine 300 mg/ml and Cabotegravir 200 mg/ml injectable
  • Rilpivirine = TMC278 = EDURANT® (NNRTI) - Tablets 25 mg once-a-day (Janssen)
  • Cabotegravir = new molecular entity = CABENUVA® (INI) (ViiV Health Care)

• Long-acting injectable nanosuspension (rilpivirine)
  • Physical/pharmacological properties, Baert et al. 2009
  • Stabilizing excipients, tolerability, Chamanza et al. 2017
  • Once-a-month, i.m. injection
  • LA formulation potential to improve convenience
  • PIP EMA decision P/0312/2017; studies in 12-18 y; 2-12 y

• NDA and MAA submitted 2019
Age-appropriate formulations NTDs:
• Manage, reduce complexity
• Supply chain; local manufacturing
• Access/Costs
• Solids
• WHO prequalification
• Partnerships


Klingmann V, “Acceptability of Mini-Tablets in Young Children: Results from Three Prospective Cross-over Studies” AAPS Pharm Sci Tech, 18 (2) 263-266 (2017)


THANK YOU!

QUESTIONS?

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