

Bend Biomedical, Nonprofit Global Health Pharmaceuticals
Lymphatic Filariasis Blister Packaging in India Concept Note
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PROJECT TITLE

Single-drug blister packs of preventive chemotherapy for hotspots of lymphatic filariasis in India

FUNDS REQUESTED

Total costs BMGF: \$2,209,280

Total costs USAID: \$2,209,280

FOREWORD

In India, more than 23 million people are currently infected with lymphatic filariasis (LF).^{1,2} Most live in urban LF “hotspots” with low sanitation and poor hygiene.^{3,4} Under National Vector Borne Disease Control Program (NVBDCP), the Government of India (GOI) has been implementing Mass Drug Administration (MDA) as a preventive intervention against LF in the form of triple drug preventive chemotherapy (PC) administered to the susceptible population. MDA consumption coverage has often been suboptimal, especially in hotspots, and one of the most important reasons is often lack of acceptance. Because LF PC is dispensed as loose tablets from shared bottles, and on regular paper without labels or instructions,⁴ beneficiaries often do not trust the medicines distributed by the health care workers.⁵ This phenomenon seems to be more acute in urban slums, where health systems are weaker.⁶ This proposal is a response to the call for steps to be taken to attain more effective treatment coverage in these areas.⁶

COVID has also caused harm because it has disrupted many MDA efforts. Compared to 2019, 2020 resulted in 34% fewer people receiving treatment for LF worldwide.⁷ For safety reasons, some MDA has been temporarily stopped for a considerable period, and those starting up again have slowed because of safety precautions. The resulting resurgence in LF transmission will extend the time of MDA and may extend the number of MDA rounds required to reduce infection levels below elimination thresholds.⁷

India has already missed three LF elimination targets – one in 2015, one in 2017, and one in 2021. A World Health Organization (WHO) worker recently noted that if current trends are any indication, India will not be able to eliminate the disease sooner than 2029,⁸ even with triple therapy.

PURPOSE

This concept note is a plan to develop and manufacture generic blister packs for lymphatic filariasis mass drug administration to improve acceptance in slum areas of India. After development, we plan to manufacture 60 million blister-packed tablets of ivermectin (IVM), 45 million blister-packed tablets of diethylcarbamazine citrate (DEC), and 15 million blister-packed caplets of albendazole (ALB). This amount is sufficient for triple therapy of 5 million people for 3 years of any age and height in India. The timeframe for delivery from our partner, [REDACTED], is 16 months from the beginning of drug development through first product delivery. The development phase will take 14 months, while the manufacturing phase will take another 2 months for 3 years. We estimate delivery of the product before the MDA round in January 2024. A supply chain has already been established.⁹

Second, when these blister packs are distributed, to conduct a study to determine whether the reason for poor acceptance and effectiveness in urban hotspots in India is due to the nature of the packaging. The comparison will be standard of care (loose pills in ordinary paper with no labels or instructions) vs. blister packs with drug name and dosage on the reverse, pill colors, drug purpose, instructions and side effects printed on inserts in the language decided on by NVBDCP—likely English or Hindi.

BACKGROUND

Lymphatic filariasis is a poverty-related disease that impairs or permanently disables millions of people every year, often resulting in life-long physical pain and social stigmatization. Helminths (parasitic worms), carried by mosquitoes, cause the disease primarily by attacking the lymphatic system. The infection usually begins in childhood, with approximately one-third of children in endemic areas infected before age five.¹⁰ In children the disease presents with adenitis and adenopathy. Starting after puberty, adult clinical symptoms include permanent lymphatic system, liver, and kidney damage, sometimes leading to death. In later stages, the disease causes recurrent secondary bacterial infections hastening a hardening and thickening of the skin, known as elephantiasis.

MDA is a key strategy in fighting against LF, approved globally to prevent lymphatic filariasis in endemic areas and requires administration to all the susceptible population in the community once or twice a year. MDA decreases transmission rates and prevents progression from subclinical to clinical disease and worse morbidity.¹¹ In the past, the primary drug diethylcarbamazine, or else drugs ALB and DEC combined were used for this purpose. In 2017, new recommendations¹¹ for eliminating the disease were published by the World Health Organization (WHO) and funded by the US Agency for International Development (USAID). Depending on special criteria and on co-endemic loiasis or onchocerciasis, there are four recommended treatments: annual triple therapy of ALB, DEC, and IVM (a combination used in most of India); annual dual therapy of ALB and IVM; annual dual therapy of DEC and IVM; or biannual ALB alone.

PROBLEM

The current approach of PC in India is for most tablets to be distributed from shared bottles and often given out in ordinary folded paper without labels or instructions. As a result, patients do not trust the medicines. The consequences are effective coverage between only 23.0% and 50.3%⁴ in urban slums. Because the drugs are being supplied to governments at no or low cost, and through a

guaranteed contract such as to GOI, the makers are unwilling to change the packaging or otherwise improve products, and they are reluctant to allow the product to leave their direct control to be blister-packaged elsewhere.

SOLUTION

The solution is to manufacture low-cost, single-drug blister packs of generic ivermectin 3 mg (200 mcg/kg dose—or by height in India), DEC 100 mg (6 mg/kg dose—or by age in India), and ALB (400 mg dose), and supplement the sales with grants from governments (e.g., USAID), foundations (e.g., Bill and Melinda Gates Foundation, BMGF), charitable contributions, and sale on the commercial market. This nonprofit model will make blister packs that are WHO “prequalified generics” and an improvement from existing drugs in use now. India already uses blister packs for leprosy (National Leprosy Eradication Programme) and tuberculosis (National Tuberculosis Elimination Programme). We suggest adding filariasis (Elimination of Lymphatic Filariasis) to this group.

Large cartons designed specifically for this project will be used by [REDACTED] to reduce cost of manufacturing. The cartons will be 200 tablets IVM (20 x 10's), 1000 tablets DEC (100 x 10's), and 100 caplets ALB (10 x 10's). After the first manufacturing run, a redesign will allow for standard size cartons to be made with different packaging (other than just LF PC) to be sold competitively to consumers.

INNOVATIONS

Our primary innovation is blister packaging PC for MDA of lymphatic filariasis, improving pills in bottles from free-drug manufactures. Secondly we are adding three different colors to the ordinarily white tablets and caplets to help differentiate pills for people who cannot read. Finally, we are individually labeling all medicines and providing informative literature inside the cartons to include drug purpose, instructions and possible side effects, in the appropriate languages.

EXTENDED TARGETS AND OTHER BENEFITS

In addition to treating lymphatic filariasis (51 million currently infected worldwide), our blister-packed LF medicines alone or in combination can treat two other MDA diseases: onchocerciasis (25 million) and soil-transmitted helminthiasis (ancylostomiasis, ascariasis, and trichuriasis, combined >1 billion). The same drugs can be used for PC for these diseases, and one or more are prescribed¹² for loiasis, mansonelliasis, oesophagostomiasis, scabies, strongyloidiasis, and tropical pulmonary eosinophilia.¹³

The benefits of blister packaging these drugs extend beyond providing labels and instructions. Blister packaged medicines are perceived as trustworthy. They are moisture-protected, tamper-proof, child safe, individually labeled, and environmentally friendly, in comparison to plastic bottles.¹⁴ A paper on this topic and meta-analysis of MDA acceptance and effectiveness studies in India is forthcoming.

ACCEPTANCE AND EFFECTIVENESS STUDY

Our acceptance and effectiveness studies will evaluate single-drug blister packs vs loose pills for lymphatic filariasis PC in an urban district with slum areas. The new formulation could be piloted in selected areas, and using a control arm, the coverage of MDA with the new formulation could be compared to the same for the conventional formulation. Further it could also be interesting to examine the number of people who have never been treated who agree to be treated precisely because of the blister packs. The models tell us that if the proportion of non-compliant (never treated) declines, treatment will be more effective. The existing drug formulation for LF MDA

consists of pills in bottles: IVM 3 mg at 200 mcg/kg (or height), DEC 100 mg at 6 mg/kg (or age), and ALB 400 mg. The trial formula is the same, but the tablets are in single-drug blister packs. All bottled drugs during routine MDA rounds in the control arm will come from the name-brand free-drug manufacturers: MSD, Eisai, and GSK. Households will be selected for each arm, and eligible participants will receive one or the other formula. The number of compliant patients in each arm and mean microfilariae Mf% using night blood survey and filarial test strips after treatment will be compared.

TIMELINE

We will be able to start the intervention in time for MDA 16 months from the start of the project. There is a 14-month development phase for the tablets and caplet at [REDACTED]. The first round of products will be ready by at least December 2023. Then two more years of IDA PC are required to assure coverage for the treated patients.

Year 1: MDA January & February 2024, 5 million* people treated with blister packed triple therapy; Acceptance and effectiveness study 1

Year 2: MDA January & February 2025, 5 million* people treated with blister packed triple therapy; Acceptance and effectiveness study 2

Year 3: MDA January & February 2026, 5 million* people treated with blister packed triple therapy; Acceptance and effectiveness study 3

* Same geographic location

FUNDING

The total funding of the project will be shared by BMGF and USAID and is \$4,418,560. This funding accomplishes the development phase, manufacturing rounds, and studies of this proposal, and is divided into grants from BMGF \$2,209,280, and USAID \$2,209,280.

The blister pack per dose manufacturing costs to us are 8.9 cents to treat a (short) child with all three drugs, up to 15.6 cents to treat a (tall) adult with all three drugs. This does not include warehousing and shipping. Note that the most pills any adult would receive is 8 pills. Manufacturing cost of generic IVM is 0.696 cents per tablet, generic DEC is 0.948 cents per tablet, and generic ALB is 3.622 cents per caplet. The additional cost for blister packaging per pill is 0.491 cents, 0.615 cents, and 2.519 cents, respectively.

A breakdown of the costs below includes warehousing and shipping costs in Mumbai to the MDA area(s). We estimate these costs at \$500,000 for the first year and \$250,000 for subsequent years, (0.63 cents per tablet and 0.32 cents per tablet, respectively).

Our overhead is very low: 1.68%. This is because most of us are unpaid. Overhead items are a parttime coordinator/secretary, bookkeeper, consultant, and multilingual editor, as well as for planning future projects, insurances, and supplies.

BUDGET DETAILS

Generics and blister pack development, Ahmedabad and Pithampur, to be paid by 50% BMGF and 50% USAID:

IVM \$289,547

DEC \$290,299

ALB \$293,709

Total: \$ 873,555

Year 1 Manufacturing, Mumbai, to be paid by 50% BMGF and 50% USAID:

20 million IVM tablets blister-packed \$238,000 (1.19 cents per blister-packed tablet)
15 million DEC tablets blister-packed \$234,000 (1.56 cents per blister-packed tablet)
5 million ALB caplets blister-packed \$307,000 (6.14 cents per blister-packed tablet)
Warehousing and shipping \$500,000
Total: \$1,279,000

Year 2 Manufacturing, Mumbai, to be paid by 50% BMGF and 50% USAID:
20 million IVM tablets blister-packed \$238,000 (1.19 cents per blister-packed tablet)
15 million DEC tablets blister-packed \$234,000 (1.56 cents per blister-packed tablet)
5 million ALB caplets blister-packed \$307,000 (6.14 cents per blister-packed tablet)
Warehousing and shipping \$250,000
Total: \$1,029,000

Year 3 Manufacturing, Mumbai, to be paid by 50% BMGF and 50% USAID:
20 million IVM tablets blister-packed \$238,000 (1.19 cents per blister-packed tablet)
15 million DEC tablets blister-packed \$234,000 (1.56 cents per blister-packed tablet)
5 million ALB caplets blister-packed \$307,000 (6.14 cents per blister-packed tablet)
Warehousing and shipping \$250,000
Total: \$1,029,000

Year 1 Acceptance and effectiveness studies, area(s) to be determined by GOI, to be paid by 50% BMGF and 50% USAID:
Consultant \$30,000
Principal Investigator salary \$0
Miscellaneous \$15,000
Total: \$45,000

Year 2 Acceptance and effectiveness studies, area(s) to be determined by GOI, to be paid by 50% BMGF and 50% USAID:
Consultant \$30,000
Principal Investigator salary \$0
Miscellaneous \$15,000
Total: \$45,000

Year 3 Acceptance and effectiveness studies, area(s) to be determined by GOI, to be paid by 50% BMGF and 50% USAID:
Consultant \$30,000
Principal Investigator salary \$0
Miscellaneous \$15,000
Total: \$45,000

Direct costs: \$ 4,345,555
Indirect costs: \$ 73,005 (1.68%)
Total costs: \$4,418,560
Total costs USAID \$2,209,280
Total costs BMGF \$2,209,280

CREDENTIALS

Bend Biomedical is a 501(c)(3) nonprofit global health pharmaceutical company. Bend's mission is to manufacture, package, and distribute high-quality, low-cost medicines to treat and prevent

serious diseases around the world. We sell at or below cost, or donate outright, our blister-packed medicines in extra-large cartons to governments and organizations serving neglected populations through mass drug administration (MDA). These medicines, when distributed below cost, are funded through grants, charitable contributions, and proceeds we make by selling medicines in standard size cartons on the commercial market. For this LF project in India we are partnering with [REDACTED], a generic manufacturer and mass blister packaging firm with manufacturing facilities and offices throughout India. Our Bend Biomedical team consists of five Ph.D.s, four M.D.s, three R.N.s, and two J.D.s, with representatives from India, Nigeria, Tanzania, and USA. Our India team members are Kajari Bandyopadhyay, M.D. (Board of Advisors), Sitikantha Banerjee, M.D. (consultant, Board of Advisors), and Sunil Khanna, Ph.D. (Board of Directors). We are not a religious organization and are not trying to convert people to a particular religion.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

A written consent is not required for activities conducted under Indian national public health programs (ELF under NVBDCP for this project and study) considered beneficial to the population. The oral consent from participants will be documented by names on the data collection form, but all identifiers will be removed before analysis.

ABBREVIATIONS

ALB: Albendazole; BMGF: Bill and Melinda Gates Foundation; DEC: Diethylcarbamazine citrate; ELF: Elimination of Lymphatic Filariasis; GOI: Government of India; IDA: Ivermectin with diethylcarbamazine and albendazole; IVM: Ivermectin; MDA: Mass drug administration; Mf%: Proportion microfilaremic; NVBDCP: National Vector Borne Disease Control Program; USAID: United States Agency for International Development; WHO: World Health Organization.

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