Landscape analysis on applicator manufacturers for delivery of microbicide gels

Results from China, India, and the Republic of South Africa

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Contents

Acronyms iv
Introduction 1
Methods 1
Listing of potential manufacturers 2
Phase I (preliminary) assessment 3
Phase II (in-depth) assessment 3
Key findings 4
Recommendations 6
References 7
Appendix A. Questionnaires sent to companies 8
Appendix B. Phase I scoring criteria 10

Acronyms

AIDS	acquired immunodeficiency syndrome
CE	Conformité Européenne
CFDA	China Food and Drug Administration
CRC	Cardiorespiratory Computers cc
DMF	Drug Master File
FDA	United States Food and Drug Administration
GMP	Good Manufacturing Practice
HIV/AIDS	human immunodeficiency virus
HMC	Beijing Highway Market Consulting Co., Ltd.
HVAC	heating, ventilation, and air conditioning
ISO	International Organization for Standardization
R	South African rand
RMB	Chinese renminbi
USAID	United States Agency for International Development

Introduction

HIV/AIDS is the leading infectious cause of adult mortality worldwide.[1] Women, especially those in developing countries, bear the disproportionate burden of the epidemic. In Africa today, women are 1.3 times more likely than men to be infected with HIV, and young women aged 15 to 24 are 2.5 times more likely to be infected than young men.[2] It was estimated that at the end of 2003, 5.3 million adults and children in South Africa and 5.1 million adults and children in India were living with HIV.[3]

Microbicides, substances that could substantially reduce the transmission of HIV, are currently under development.[4] For many women who cannot negotiate condom use with their partners, microbicides represent an urgently needed woman-initiated option for HIV prevention. Many dosage forms for delivery of microbicides have been evaluated in clinical trials, including oral tablets, vaginal rings, injectables, and gels.

Prefilled, plastic, single-use applicators have been used to deliver gels in the majority of clinical trials, including the most recent phase 3 trial of tenofovir gel (HTI Plastics, Lincoln, Nebraska, United States of America).[5] However, prior research has indicated that acceptable, low-cost, user-filled applicators can be an important alternative for microbicide introduction in developing countries.[6,7] In 2005, PATH conducted a survey of manufacturers in India and South Africa, the two countries that have the greatest number of people living with HIV. Although this manufacturer scan identified two manufacturers in South Africa that could supply applicators and five applicator manufacturers in India, the scope of the search was limited and the assessment did not include manufacturing facility assessments.

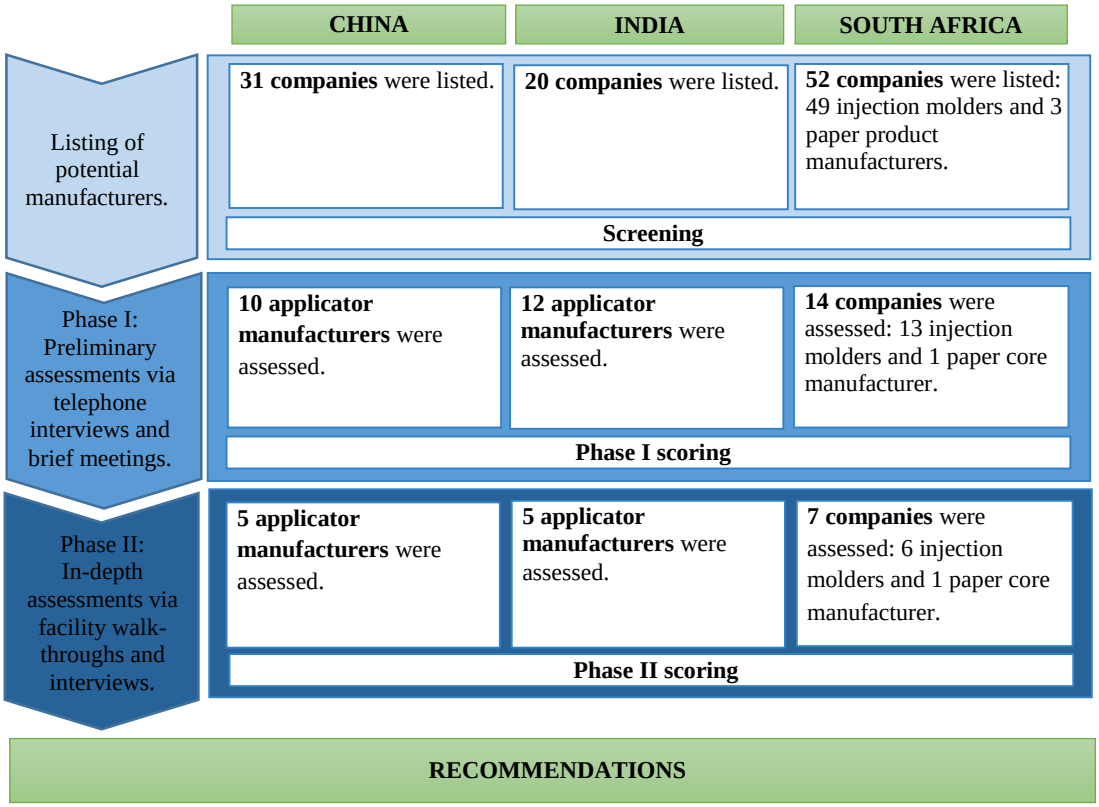
In 2014, as microbicide sponsors and developers focused their efforts more on future introduction strategies, PATH was tasked to perform a wider landscape survey of applicator manufacturers, including facility assessments in China, India, and South Africa, where a substantial number of those manufacturers are most likely located. The primary purpose of this manufacturer landscape survey was to determine whether there were additional manufacturers that could provide low-cost applicators for future introduction efforts, and if so, to identify three to five potential manufacturers in each country. We assumed that organizations that would commercialize microbicide gels would carry out in-depth assessments of potential manufacturers to identify the most appropriate manufacturer for delivery of their microbicide gel. This report summarizes the results of our assessments in China, India, and South Africa.

Methods

PATH searched for consultants/consulting firms in China, India, and South Africa that would be interested in and capable of carrying out this manufacturing scan. We identified initial candidates from a list of consultants/consulting firms with whom PATH had previously worked and then conducted telephone interviews with a shortlist of candidates. We eventually contracted with Beijing Highway Market Consulting Co., Ltd. (HMC) in China, Mediminds in India, and Cardiorespiratory Computers cc (CRC) in South Africa to carry out the assessments.

Between July and November 2014, three landscape surveys were conducted in three phases (Figure 1): (1) listing of potential manufacturers; (2) preliminary assessments through telephone interviews and brief meetings (Phase I assessment); and (3) in-depth assessments through facility walk-throughs and interviews (Phase II assessment). At the initial point of contact with companies in each country, the overall purpose and intended sharing of results from this work were explained. Telephone interviews and in-depth assessments were conducted upon agreement from companies.

Figure 1. Three phases of evaluation for manufacturer landscape surveys.



Listing of potential manufacturers

Potential applicator or pharmaceutical packaging manufacturers were added to the list based on desk research and interviews with industry experts. In this initial stage, a total of 103 companies were identified: 31 in China, 20 in India, and 52 in South Africa. A questionnaire developed by PATH was used to screen the companies for follow-up visits (Appendix A). In China, based on the responses to the questionnaire, 21 companies were eliminated; the remaining 10 progressed to Phase I assessment. Brief telephone calls and email communications were made with the 20 Indian manufacturers. Eight of these 20 companies were immediately screened out because they were found to be: (1) suppliers, traders, or distributors rather than manufacturers of applicators; (2) not interested in supplying applicators for microbicide delivery; or (3) too small. The remaining 12 companies were included in the Phase I assessment. In South Africa, 14 companies provided answers to the questionnaire and all 14 progressed to the Phase I assessment.

Phase I (preliminary) assessment

Companies that passed initial screenings were assessed based on the Phase I scoring criteria detailed in Appendix B.

- In China, ten companies were assessed. A 40-point score was used as the threshold. Seven companies met this threshold and were selected for more in-depth, onsite assessments in Phase II.
- In India, since it was difficult to obtain accurate information from telephone interviews, Mediminds visited all 12 companies to collect information through face-to-face meetings and observations of manufacturing facilities. They then scored each manufacturer based on the Phase I scoring criteria. After subsequent discussions between Mediminds and PATH, five companies were selected for more in-depth, onsite assessments in Phase II. During these discussions, results from observations of the manufacturing facilities were also taken into account to select the five companies.
- In South Africa, 14 companies were scored based on the information they provided in relation to the Phase I criteria. After subsequent discussions between CRC and PATH, eight companies (six injection molding companies, one paper core manufacturer, and one vaginal applicator manufacturer) were selected for more in-depth, onsite assessments in Phase II. During this process, more weight was assigned to International Organization for Standardization (ISO) certification when more than one company had the same score. Additionally, while we could not use the same criteria to assess the paper core manufacturing facility (since the criteria were developed primarily for injection molding companies), we felt it was important to explore their interest and possibility of manufacturing paper applicators.

Phase II (in-depth) assessment

In Phase II, companies that were selected for in-depth assessment were assessed for compliance with Good Manufacturing Practices (GMPs) and production capacity and capability. Our consultants/consulting firms also had discussions with the manufacturers to understand their distribution channels, existing clients, and interest in manufacturing and supplying their applicators for use with microbicide gels.

Two of the seven companies contacted by HMC in China to make appointments for onsite assessments declined the request because their manufacturing sites would not be available for an assessment during the time frame requested. One additional company did not manufacture applicators, contrary to the information provided; however, the owner also owns an applicator manufacturing company and the information he provided turned out to be for the applicator company. Since he strongly recommended visiting the applicator company, HMC decided to include it in their onsite assessments. Consequently, five Chinese companies were visited in Phase II.

The following section describes our key findings and recommendations.

Key findings

Our manufacturer landscape survey located several companies in China, India, and South Africa with the capacity and expertise to manufacture vaginal applicators but none that were manufacturing paper applicators.

- There were several vaginal applicator manufacturers identified in China and India. All manufactured single-use, plastic applicators using high-density polyethylene, low-density polyethylene, a combination of the two, or polypropylene. In China, both user-filled and prefilled, single-use applicators were available. In India, all manufacturers surveyed made single-use, user-filled applicators, since these could be sold at the lowest price to end-user customers in the country.
- In South Africa, only one company was manufacturing a thermoplastic, rubberized vaginal applicator for semisolid pharmaceuticals (i.e., gels or creams). The other manufacturers included in our assessment in South Africa produced injection molded or paper core products, but they would be able to produce applicators.

Many of the manufacturers surveyed in the three countries had more than one molding machine with which to make applicators or other plastic packaging products. However, the production capacity of these manufacturers varied significantly. In China, the existing production capacity for applicators ranged from 30 to 90 million per year. In India, the range was 1.5 to 8 million per year. In South Africa, one applicator manufacturer had the capacity to produce 2.4 million applicators per year.

Having ISO certification was relatively common among applicator manufacturers in China. Six of ten manufacturers assessed in Phase I had ISO certification, and all five companies assessed in Phase II had ISO certification. In contrast, having ISO certification was not common in India and South Africa. More than half of the manufacturers in India and South Africa that were assessed in Phase I did not have ISO certification (8 of 12 manufacturers in India and 8 of 13 manufacturers in South Africa). However, all five companies in India and five of seven companies in South Africa that were assessed in Phase II had ISO certification. This might be attributable to differences in how stringently manufacturers of applicators or packaging for other medical products are regulated in each country.

The China Food and Drug Administration (CFDA) has a general rule for onsite assessments of pharmaceutical packaging production. Chinese manufacturers of microbicide applicators would need a production license for drug packaging materials and containers, assuming that the microbicide and applicators were packaged together in order to ensure proper use. The production license for drug packaging materials and containers is issued by the CFDA. Manufacturers that have this license are allowed to produce and supply applicators to pharmaceutical companies, which then package their drugs with the applicators or fill the applicators with their drugs.

In India, on the other hand, no official GMP certification is applicable for vaginal applicator manufacturers, although most of the well-known manufacturers comply with GMP and/or ISO standards (ISO 9001:2008). Only a few large manufacturers had clean room facilities that complied with Class

100,000[a] standards, the level of cleanliness required for molding and blowing (pre-forming) operations for plastic containers.

Among the companies assessed, vaginal applicators for microbicide delivery could be produced at relatively low cost. Table 1 provides a range of estimated pricing for the manufacture of vaginal applicators, which were provided by several of the manufacturers assessed in the three countries. In general, the cost of an applicator is dependent on the size, design, materials, sterilization methods, taxes and duties imposed, and procurement and delivery quantity. The specific parameters for these estimates are described below in Table 1.

Table 1. Price range provided by companies.

Country	Number of companies that provided cost estimates	Type of applicator	Unit cost in US$
China	4	Plastic prefilled, single-use	0.030–0.150
India*	2	User-filled, single-use	0.470–0.600
South Africa†	4	Plastic reusable	0.029–0.085
		Plastic single-use	0.145
		Thermoplastic reusable	0.870
		Paper single-use	0.027

* India:

- The prices are ex-factory plus value-added tax and central sales tax. These taxes are exempted if products are manufactured for export.
- The development cost of a customized mold ranges from Indian Rupees (Rs.) 500,000 (US$8,333) to Rs. 700,000 (US$11,666), which is generally included in the final price to clients. Some manufacturers might charge the price of the mold up front and subsequently adjust their price to clients if additional costs are incurred.
- Costs associated with export (e.g., freight and insurance) are not included in the prices above. Freight and insurance costs are approximately US$2,500 to US$3,000 per 20-foot container.
- A 20-foot container can hold approximately 1 million applicators (325 boxes x 4,000 applicators per box). The quantity of applicators per container varies depending on the size and design of the applicators.

† South Africa:

- Cost is estimated based on a production quantity of 10-20 million.
- Capital costs include costs for designing and molding/tooling only, which ranges from US$41,000 to US$264,000, depending on existing capacity.

It was relatively common for Chinese and Indian manufacturers to export their products to other countries through traders and distributors. Three of five companies in China and four of five companies in India that were assessed in Phase II exported their products to other countries, including a few exported to European countries and the United States.

[a] Class 100,000 clean room: denotes the number of particles of size 0.5 µm or larger permitted per cubic foot of air.

Recommendations

We recommend a total of nine manufacturers for future in-depth assessment: three companies each in China, India, and South Africa (see Table 2 for key details on each).

Table 2. Key aspects of the recommended companies.

Country		Manufactures applicators	ISO certification	Facility organization and cleanliness	Exports to other countries
China	Company A	No	✓	✓	No
	Company B	Yes	✓	✓	✓
	Company C	Yes	✓	✓	✓
India	Company A	Yes	✓	✓	✓
	Company B	Yes	✓	✓	✓
	Company C	Yes	✓	✓	✓
South Africa	Company A	No	✓	✓	No
	Company B	No	✓	✓	No
	Company C	No	✓	✓	✓
Acronym: ISO, International Organization for Standardization.					

In China, two of the three recommended companies had a very well-maintained and organized facility. One of these two had a relatively compact facility but had very strong business development strategies, with research and development capability. This company was also well experienced in international trade. The third company did not manufacture vaginal applicators; however, they had already produced some samples and were applying for a production license from the CFDA. This company was regarded as the top medical packaging materials supplier in the region and had a very good reputation among pharmaceutical companies.

In India, all three recommended companies had a good level of GMP compliance; an adequate level of installed capacity; experience in manufacturing medical products, including vaginal applicators; ISO certification; business expertise; and export capability. In addition, they were interested in producing applicators for microbicide delivery for social benefit and had experience in supplying their products to health programs in the public sector.

In South Africa, all three manufacturers that we recommend are not currently producing applicators. However, we believe that they would be suitable for manufacturing injection molded products. Two of the three companies had especially clean and well-organized facilities. The third company was particularly focused on medical products. It distributed products to other countries, including the United States and countries in Europe.

The paper core manufacturer that we visited was very keen to get involved in manufacturing cardboard applicators. It was surprising to see their highly competitive quotation for a cardboard applicator, even though the company will need to invest in equipment and other facility modifications to initiate applicator

manufacture. This company could be a good candidate for further in-depth assessment, assuming that proper technical assistance could be provided to develop and manufacture cardboard applicators.

References

1. World Health Organization (WHO). *Facts and Figures: The World Health Report 2003—Shaping the Future*. Geneva: WHO; 2003.
2. United Nations Population Fund (UNFPA). *State of World Population 2004: The Cairo Consensus at Ten: Population, Reproductive Health and the Global Effort to End Poverty*. New York: UNFPA; 2004.
3. Joint United Nations Programme on HIV/AIDS (UNAIDS). *2004 Report on the Global AIDS Epidemic*. Geneva: UNAIDS; 2004.
4. International Partnership for Microbicides. IPM Product Pipeline. Available at: http://www.ipmglobal.org/products-development.
5. Rees H, Delany-Moretlwe SA, Lombard C, et al. FACTS 001 phase III trial of pericoital tenofovir 1% gel for HIV prevention in women. To be presented at: Conference on Retroviruses and Opportunistic Infections, February 22–25, 2016; Boston, Massachusetts. Abstract available at: http://www.croiconference.org/sessions/facts-001-phase-iii-trial-pericoital-tenofovir-1-gel-hiv-prevention-women.
6. Cohen JA, Brache V, Foster J, Cochon L, Callahan M, Schwartz J. A randomized, comparative safety study of a prefilled plastic and user-filled paper applicator with candidate microbicide tenofovir 1% gel. *Sexually Transmitted Diseases*. 2013;(40)6:476–481.
7. Cohen JA, Steele MS, Urena FI, Beksinska ME. Microbicide applicators: understanding design preferences among women in the Dominican Republic and South Africa. *Sexually Transmitted Diseases*. 2007;34(1):15–19.

Appendix A. Questionnaires sent to companies*

Questionnaire used in China

1. Number of years company has been in business.
2. Annual company revenue (if possible).
3. Products company manufactures (in addition to applicators).
4. Types of applicators produced (i.e., user-filled, prefilled, single-use, reusable) and materials used in their manufacture (e.g., plastic, paper, other).
5. Indications for use, regulatory approval status, and pricing of applicators.
6. Quantity of applicators company produces annually.
7. Current operational capacity and maximum capacity for applicators.
8. Manufacturing standards with which company complies.
9. Distribution channels company uses for applicators and other products.
10. Names of countries to which company exports applicators.

Questionnaire used in India

1. Number of years company has been in business.
2. Corporate structure and ownership.
3. Annual company revenue (if possible).
4. Products company manufactures (in addition to applicators).
5. To whom applicators are supplied (if this information can be shared by the manufacturer).
6. Own products versus agencies (as a proxy for internal research and development focus).
7. Information related to patents held on applicators, if any (functional and/or design), and on trademarks, if applicable.
8. Types of applicators produced (i.e., user-filled, prefilled, single-use, reusable) and materials used in their manufacture (e.g., plastic, paper, other).
9. Indications for use, regulatory approval status, and pricing of applicators.
10. Quantity of applicators company produces annually.
11. Manufacturing standards with which company complies.
12. Distribution channels company uses for applicators and other products.
13. Names of countries to which company exports applicators.
14. History of company's collaboration with the public health sector.

Questionnaire used in South Africa

1. Number of years company has been in business.
2. Corporate structure and ownership.
3. Annual company revenue (if possible).
4. Experience in manufacturing applicators.
5. Medical products manufactured by the injection molding process (in addition to applicators).
6. Materials used to injection mold medical products.
7. To whom the medical products are supplied (if this information can be shared by the manufacturer).
8. Sizes of injection molding machines.
9. Experience in manufacturing any products using a 3D printer (whether an additive manufacturing process is done by another company).
10. Own products versus agencies (as a proxy for internal research and development focus).
11. Information related to patents held, if any (functional and/or design), on medical products and on trademarks, if applicable.
12. Indications for use, regulatory approval status, and pricing of medical products.
13. Manufacturing standards with which company complies.
14. Capability to assemble medical products in-house.
15. Capability to manufacture packaging in-house.
16. Distribution channels company uses for its medical products.
17. Names of countries to which medical products are exported.
18. History of collaboration with the public health sector.

* Note: Questionnaires used in the three countries are slightly different partly because there are applicator manufacturers in China while there are only injection molding companies and paper core product manufacturers in South Africa. In addition, some of the questions that were asked in South Africa in the initial stage were incorporated into the Phase I assessment in China.

Appendix B. Phase I scoring criteria

	Criteria	China	India	South Africa
1	Number of years in business	>10 years=5; 5–10 years=3; <5 years=1		
2	Corporate structure	N/A		
3	Annual revenue (if possible)	>RMB 40 million=5; RMB 10–40 million=3; <RMB 10 million=1	>US$5 million=5; US$1–3 million=3; <US$1 million=1	>R10 million=5; R 5–10 million=3; <R 5 million=1
4	Experience in applicator manufacturing	Yes=2; No=0		
5	Experience in manufacturing medical products (e.g., semisolid pharmaceuticals) by the injection molding process	Yes=5; No=0		
6	Number of materials used for injection molding of medical products	>10=5; 5–10=3; <5=1		
7	To whom the medical products are supplied	Local and international sales=5; Local sales only (or international sales through other agencies)=2		
8	Sizes of injection molding machines	At least 2 machines between 50 and 100 tons=5; 1 machine between 50 and 100 tons=2; No machines between 50 and 100 tons=0		
9	Experience in manufacturing products using the 3D printing and/or additive manufacturing process through another company	Yes=3; No=0		
10	Develops own products versus serves as contract manufacturer (as a proxy for internal research and development focus)	Develops own products + contract manufactures=4; Own products only=3	Has in-house design capability: Yes=3; No=0	Develops own products + contract manufactures=4; Own products only=3
11	Intellectual property (functional and/or design) generated/held (if any) on the medical products, including trademarks if applicable	Company has generated own intellectual property=4; Company has not generated own intellectual property=0		
12	Types of medical products produced	>4 products=5; 1–4=1–4		
13	Regulatory approval status	CE, FDA, and other country certification=5; CE, FDA, or other country certification=2	Submitted to DMF (United States) or countries with stringent regulatory bodies=5; Not submitted to DMF or other stringent regulatory bodies=0	CE, FDA, and other country certification=5 CE, FDA, or other country certification=2
14	Manufacturing standards complied with	ISO 13485 and other ISO=5; Other ISO=3; None=0	ISO 2008 and other ISO=5; Other ISO=3; None=0	ISO 13485 and Other ISO=5; Other ISO=3; None=0
15	Has clean room/air handling unit (HVAC)	---	Has clean room and HVAC=5; Has clean room only=3; Clean but neither clean room nor HVAC=2; Not clean=0	---
16	Assembles products in-house	Yes=4; No=2		

	Criteria	China	India	South Africa
17	Packages products in-house or externally	In-house packaging capacity=5; No in-house packaging capacity=0		
18	Distribution channels used for medical products	Local and export channels=5; Only local channels=2		
19	Number of countries to which medical products are exported	>4 countries=5; 0–4 countries=0–4	---	>4 countries=5; 0–4 countries=0–4
20	History of collaboration with the public health sector	Yes=3; No=0		

Note: CE (CE mark), for sale in the European Economic Area: signifies that the product has been assessed to meet high safety, health, and environmental protection requirements

Acronyms: CE, Conformité Européenne; DMF, Drug Master File; FDA, United States Food and Drug Administration; HVAC, heating, ventilation, and air conditioning; ISO, International Organization for Standardization; R, South African rand; RMB, renminbi.