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HNP DISCUSSION PAPER

Exploratory Study on Active Pharmaceutical Ingredient Manufacturing for Essential Medicines

Janet Bumpas and Ekkehard Betsch

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Health, Nutrition and Population (HNP) Discussion Paper

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Health, Nutrition and Population (HNP) Discussion Paper

EXPLORATORY STUDY ON ACTIVE PHARMACEUTICAL INGREDIENT MANUFACTURING FOR ESSENTIAL MEDICINES

Funded by a grant from DFID under the Medicines Transparency Alliance pilot program

Abstract: Active Pharmaceutical Ingredients (API) of good quality are core to the manufacturing of effective and safe essential drugs. The price of APIs is the main cost driver for manufacturing. Only a limited number of large manufacturers of finished pharmaceutical products have their own API manufacturing capabilities, and none of them can make all required APIs in-house. The majority of manufacturers, including all those located in Sub-Saharan Africa (with the exception of one company in South Africa) have to buy all APIs in the open market. The paper tries to make the structures of the API market more transparent, trying to determine how difficult it is for small manufacturers in developing countries to navigate the global API market and ensure that they get a quality product at a fair price. It also looks into the competitiveness of the market, trying to assess the risk that manufacturers or traders monopolize parts of the API market for essential medicines with low commercial attractiveness. The author confirms the initial assumption that the API market provides a challenge in particular to small manufacturers, who have limited means to verify the quality of the APIs they are buying. One potential way to address this problem would be to broaden the WHO Prequalification system to include APIs for drugs that are on the WHO Model List for Essential Medicines.

Keywords: essential medicines, essential drugs, prequalification, API (Active Pharmaceutical Ingredients), local manufacturing of pharmaceuticals

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List of Acronyms

Acronym	Definition
ACT	Artemisinin-based Combination Therapy
ANDA	Abbreviated New Drug Application
API	Active Pharmaceutical Ingredient
ARV	Anti-Retro Viral
cGMP	current Good Manufacturing Practice
CHAI	Clinton HIV / AIDS Initiative
DMF	Drug Master File
EDMF	European Drug Master File
GDF	Global Drug Facility
GLC	Green Light Committee
GMP	Good Manufacturing Practices
IFC	International Finance Corporation
ISO	International Standards Organization
MMSS	Malaria Medicines Supply Service
MNC	Multi National Corporation
MSF	Médecins Sans Frontières
NAFDAC	National Agency for Food and Drug Administration and Control (Nigeria)
NDA	New Drug Application
OTC	Over The Counter
PEPFAR	President's Emergency Plan For AIDS Relief
PIC/S	The Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme
PQ	Prequalification
PZQ	Praziquantel
SFDA	State Food and Drug Administration (China)
SOE	State-Owned Enterprise (China)
SRA	Stringent Regulatory Authority
TRIPS	Agreement on Trade Related Aspects of Intellectual Property Rights
USFDA	United States Food and Drug Administration
WHO	World Health Organization
WTO	World Trade Organization

Executive Summary

Active Pharmaceutical Ingredients (APIs) are integral components of both the quality and the cost of pharmaceutical goods[a]. Equality of access for developing country final formulators to high quality essential medicine APIs should be pursued as a public health goal. This requires looking at the API market from a sustainability and quality perspective as well as from a price perspective. As every specific API market is diverse, each API market should be examined individually to determine if it is competitive with affordable prices. If it is not, specific market's problems should be articulated so that corrective action that can be taken.

Pharmaceutical manufacturing occurs in two general steps. First, firms convert raw materials into APIs. Then, firms create final formulations by mixing APIs and excipients (other non-active ingredients), pressing the mixture into tablets, or filling capsules or preparing solutions, and then packaging the product for the consumer market. For the purposes of this paper, final formulations will refer to the second stage of pharmaceutical manufacturing and not the entire process.

Firms either sell APIs on the open market ("merchant market") or use them to do their own final formulations manufacturing. Firms that manufacture both APIs and final formulations will usually still buy and sell APIs on the merchant market.

Generally speaking, the API market is very competitive with many producers. As a result, API manufacturers specialize and target their manufacturing based on a combination of the market opportunities and firm skills. Driven by lower costs, API manufacturing has slowly been shifting from the historical leaders in Western countries to newer firms in India and China.

Several regulatory authorities are involved to ensure that firms manufacture APIs and final formulations in a quality manner. The geographic location of the manufacturer and market as well as the financing source determines which regulatory agencies are involved. APIs that are intended for final formulations in sub-Saharan Africa are often less regulated due to weaker national regulatory agencies and cost-sensitive markets.

For example, sub-Saharan Africa has many final formulators, mostly in South Africa, Nigeria, Kenya, and Ghana. Firms here produce almost $1B in final formulations per annum and the International Finance Corporation (IFC) expects this number to grow. Most of these final formulation manufacturers, with the prominent exception of South Africa, manufacture non-complex, high volume, essential products, such as basic analgesics, simple antibiotics, antimalarial drugs, and vitamins. They tend not to manufacture more complex / expensive drugs because the demand for more expensive drugs is weak, cheaper drugs have lower working capital requirements, and Over The Counter (OTC) branded drugs have a higher profit potential.

[a] On average, 40-50% of the cost of goods sold for generic oral solids comes from APIs

A large question for the global public health community (including donors, technical assistance agencies and pharmaceutical manufacturers) therefore is where these final formulators procure APIs and how they ensure quality. Oftentimes, Sub-Saharan African final formulators outside South Africa procure unregulated APIs from India and China because they themselves operate in cost-sensitive and under-regulated markets. These firms can find that navigating global API markets is challenging.

API markets operate relatively efficiently. However, lack of transparency in the market and an insufficiency of manufacturers are two potential challenges that may impede equality of access to quality APIs for small final formulators in developing countries. API manufacturers may leave a market when market prices move too low, markets are too small, or economies of scale leave only a few dominant firms.

In order to improve the probability that a well-intentioned final formulator in low- and middle-income countries (LMIC) in general, and sub-Saharan Africa in particular, can successfully procure high quality APIs at a low cost, the global community should:

- Train LMIC final formulators in selection, due diligence and procurement of APIs
- Improve and strengthen API regulatory capacity.
- Move forward with the WHO initiative to prequalify APIs.
- Work for healthy, sustainable, competitive API markets through procurement tactics.
- Increase API market transparency.

Drug manufacturers need to be partners in this endeavor and make some changes as well. These include gaining regulatory approvals, learning API procurement skills and acquiring testing facilities.

Further analysis and study is required to determine the best course of action.

Objective

This exploratory study was carried out to provide an overview over the present status of the API industry, in particular in India and China. It is also intended to identify risks to the supply of affordable, high quality APIs required for the manufacture of essential drugs by local generics manufacturers in countries without API production, particularly in but not limited to Africa. Funding for this study was provided by the Medicines Transparency Alliance.

Methods

This four week project was completed between May and June 2009. Both secondary research and interviews with industry leaders and analysts were conducted to identify key drivers and fragilities in the API market. Appendix One contains a list of interviewees.

Pharmaceutical Manufacturing: Active Pharmaceutical Ingredients and Final Formulations

Pharmaceutical manufacturing occurs in two general steps. First, firms convert raw materials into Active Pharmaceutical Ingredients (APIs). API production is a highly sophisticated, technically demanding chemical and biochemical fermentation and/or synthesis process. APIs constitute a significant portion of the total cost for a drug. For example, on average, 40-50% of the cost of goods sold for generic oral solids comes from APIs.[1] Commodity API manufacturing tends to be a high-volume, low-margin business where economies of scale play an important role. The average commodity API profit margin is less than 10%. In fact, many large bulk API exporters from India work with a 3% margin on exported products.[2]

The second step in pharmaceutical manufacturing is the final formulation of the drugs. Unlike the chemical business of API production, final formulations belong to the manufacturing sector. During this process, firms first mix APIs and excipients (other non-active ingredients), then either press the mixture into pills and tablets or prepare powders for solutions or filling of capsules, and finally, package the product for the public or private market. For the purposes of this paper, final formulations will only refer to this second phase of pharmaceutical manufacturing and not the entire process. Final formulations require different skills and equipment than does API manufacturing. Economies of scale matter, but less so than for API manufacturing[b] as manufacturers can produce fifty or more final formulations in a single plant with adaptable equipment.[3] Profit margins for final formulations average 20-30%.[4]

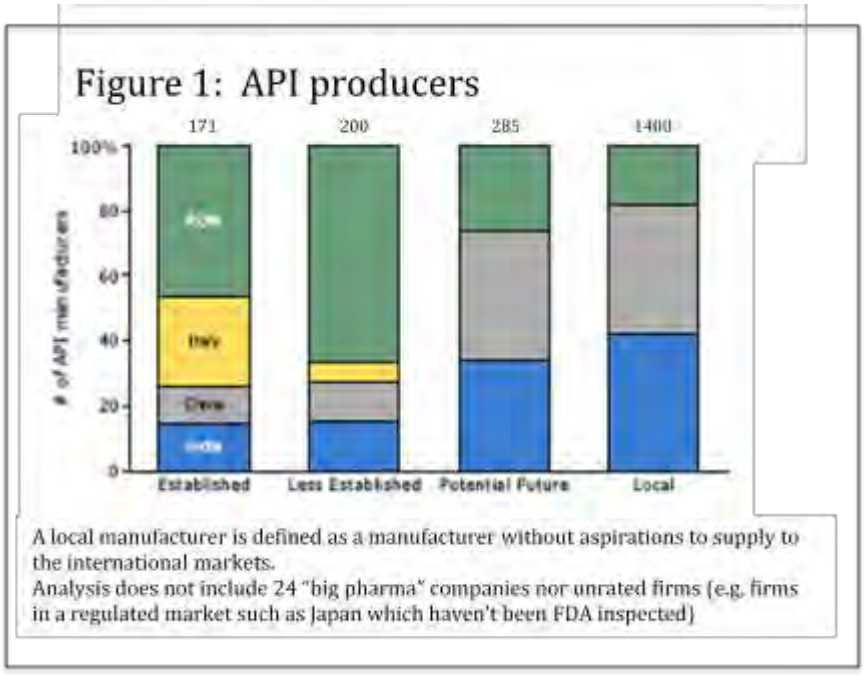
Firms either sell APIs on the open market ("merchant market") or use them to do their own final formulations manufacturing. In 2005, the total world API market was $76B and growing at an average annual rate of 8.2% (with generics growing at 10.9%). Forty one percent of APIs were sold in the merchant market and generics comprised 43.5% of the total merchant market. In 2005, final formulating firms in North America purchased 42% of APIs sold in the merchant market (75% of which

[b] This is true for most drugs. However, cGMP requires that some drugs be manufactured in separate facilities. For example, Beta-Lactams (a broad class of antibiotics that include penicillin derivatives, amoxicillin and ampicillin), would taint other products and therefore requires dedicated manufacturing, processing and primary packing (both at the API and final formulations level).

were branded), firms in Western Europe purchased 19% (62% of which were branded), and firms in Asia purchased 21% (35% of which were branded).[5]

Firms that manufacture both APIs and final formulations will still buy and sell APIs on the merchant market - one firm cannot possibly manufacture every API it needs to manufacture all its final formulations[6] and a broad portfolio of APIs does not usually translate into economies of scale.[7] Furthermore, the API division of an integrated firm tends to be oriented towards the external API market. For example, Dr. Reddy's, an Indian firm that manufactures both APIs and final formulations, charges internal pricing on its APIs (e.g. if the final formulations division of Dr. Reddy's wants to use an API manufactured at a Dr. Reddy's plant, it will have to pay the API division an internal transfer price). The API team receives bonuses for profitability so, if they can get a higher price by selling on the merchant market, the company incentives are structured for them to consider this.[8] Matrix Laboratories, (an Indian firm that is currently becoming a wholly-owned subsidiary of Mylan Pharmaceuticals, a US firm)[9] that manufactures both APIs and final formulations for HIV drugs provides another example. Matrix also sells some of the HIV APIs it manufactures to Indian final formulation competitors.[10]

In general, the API market is very competitive and has many producers. Figure 1, below[11], breaks down the number of firm by geography and level of sophistication. These 2,056 firms have 3,700 manufacturing sites globally.[12]



With so many API producers, API manufacturers have specialized and target their manufacturing based on a combination of the market opportunities and firm skills. Some examples of targeting strategies follow (list is non-exhaustive):

- ***Timing patent expirations:*** APIs for drugs that have recently come off patent in developed countries. Firms can often achieve high profit margin with these drugs. As more and more firms pick up the newly off-patent drug, the cost will slowly fall back to marginal production cost.
- ***Mastering complex manufacturing:*** Complex APIs for drugs in developed countries are often difficult for firms to manufacture and provide a barrier to entry.
- ***Exploiting gaps in the patent coverage:*** As an innovator firm must register its drug in a country to receive patent protection, some firms can exploit gaps in a drug's patent coverage.
- ***Targeting major program drugs:*** APIs for major program drugs (e.g. HIV/AIDS, TB, and Malaria) for developing countries often have significant international funding. As firms needs to have WHO PQ or Stringent Regulatory Authority (SRA) approval to qualify, this limits competition while allowing firms to get large-volume orders.
- ***Competing in generic bulk drugs:*** APIs for older drugs sold in developing countries usually have few barriers to entry and firms can operate on thin margins while still achieving significant revenues through scale.

Manufacturing moves to India and China

API manufacturing has slowly been shifting from the historical leaders in Western countries to newer firms in India and China. This trend will continue as the Indian and Chinese API industries are growing at nearly 19.3% and 17.6% annually.[13] While Italy still remains the world market leader in APIs destined to sectors such as cardiovascular or the central nervous system, China leads in anti-infective APIs with approximately 43% of world market share.[14] Table 1[15] below summarizes the manufacturing and export of APIs from India and China.

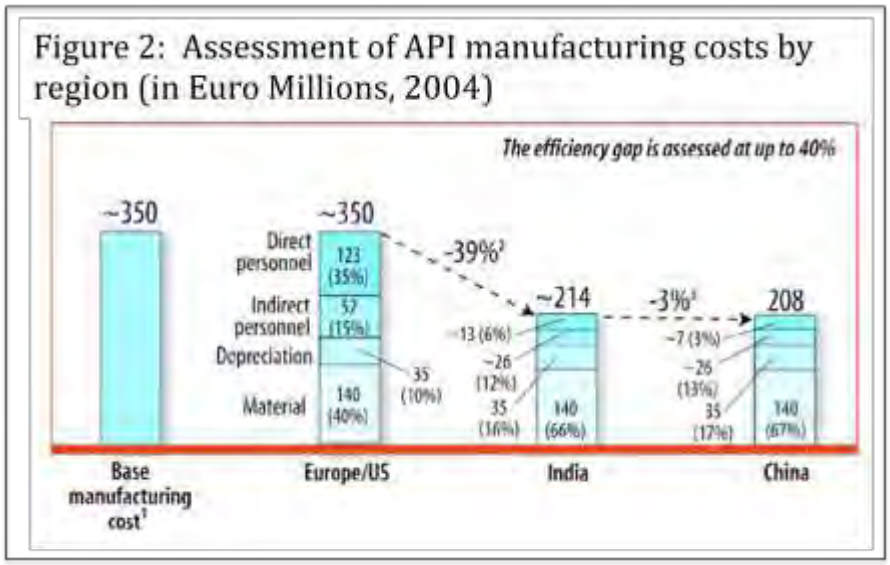
Table 1: Active Pharmaceutical Ingredient production by country

Country	Total API Production	Generic API Production	Exported APIs as % of Total API
India	$2.0B	$1.8B	75%
China	$4.4B	$4.2B	77%

Lower production costs in India and China drive much of this growth. For example, to develop, test, manufacture and market a generic medicine in India costs 20-40% of what it costs in the West.[16] Indian and Chinese advantages typically come from:

- ***Lower labor, infrastructure, transportation and equipment costs:*** If a typical Western API company has an average wage index of 100, this index is as low as 10 for the typical Indian API firm and 8 for a Chinese one, respectively. Not even the higher productivity of a Western company (due to the higher average automation level of the manufacturing processes) can annul the labor cost

difference.[17] Figure 2,[18] below, shows some of these differences. Additionally, India and China have lower electricity, coal, and water costs.[19] Indian and Chinese firms are also embedded in a network of raw materials and intermediary suppliers and so have lower shipping and transaction costs for raw materials. Firms is these two countries often use less expensive equipment, leading to a lower depreciation cost.



- ***Fewer environmental regulations:*** Currently, Indian and Chinese firms have fewer environmental regulations regarding the buying, handling, and disposing of toxic chemicals, which lead to lower direct costs for these businesses. However, as India and China increase environmental stringency, firms will have to bear more of these costs.
- ***Larger scale manufacturing:*** The IFC estimates that a factory making tablets in blister packaging needs to manufacture around 1.0–1.5 billion tablets per year to be said to be operating at scale. Indian and Chinese firms have often reached scale when firms in other countries have not. For example, the IFC estimates that a third of the 30–40 percent cost disadvantage that a leading Ghanaian final formulations manufacturer suffers versus high-scale Indian manufacturers is attributable to scale.[20]
- ***Lower barriers to market entry*****:** Market contestability in India and China is discussed in detail in section 6.

As a generalization, Chinese firms have tended to focus on the earlier raw materials stage whereas Indian firms have tended to focus more on the final API manufacturing stage. In many cases, a Chinese firm will make the raw material for a pharmaceutical product and then sell it to an Indian firm who will then convert the raw material into an API. Then, either the same firm, another Indian firm, a global Multinational Corporation (MNC) or a final formulator in a developing country will convert the API into a final formulation product ready for the market. However, the

situation is rapidly evolving as both China and India gain new manufacturing skills.

Not surprisingly, while many Western API firms have been winding down and/or consolidating their manufacturing capacity, many firms in India and China have been increasing capacity to meet the growing demand. Indian firms interviewed were not concerned about physical manufacturing capacity as a limiting factor. In fact, if demand increases at a faster than expected pace, a good Indian API manufacturer can build a new plant and get required regulatory approval in about 18 months.[21]

More information on China and India and their API manufacturing capabilities can be found in Appendixes Two and Three.

Regulation of Active Pharmaceutical Ingredient industry

Several regulatory authorities can be involved in ensuring that firms manufacture APIs and final formulations in a quality manner. Table 2, below, shows that the financing source as well as the geography of the manufacturer and market determines which regulatory agencies are involved. Currently, the agency that regulates the final formulation has the most power in keeping low quality APIs away from consumers.

Table 2: Scope of authority for Regulatory Agencies

	API producing country	**Final formulation producing country**	**Financing source**	**Minimum required regulatory authority for API**	**Minimum required regulatory authority for final formulation**
1	Local	Local	Local	Local government	Local government
2	International Producer	Local	Local	International producing country and local government	Local government
3	International producer	International producer	Local	International producing country and local government	International producing country and local government
4	Any	Any	Inter-national assistance	WHO PQ or SRA	WHO PQ or SRA

In the first case, if the API and final formulation are locally manufactured and financed, the local regulatory authority is the only regulatory body involved. If this scenario occurs in e.g., the United States, then only the USFDA regulates. If this scenario occurs in e.g., Nigeria, then only the National Agency for Food and Drug Administration and Control (NAFDAC) regulates the drug.

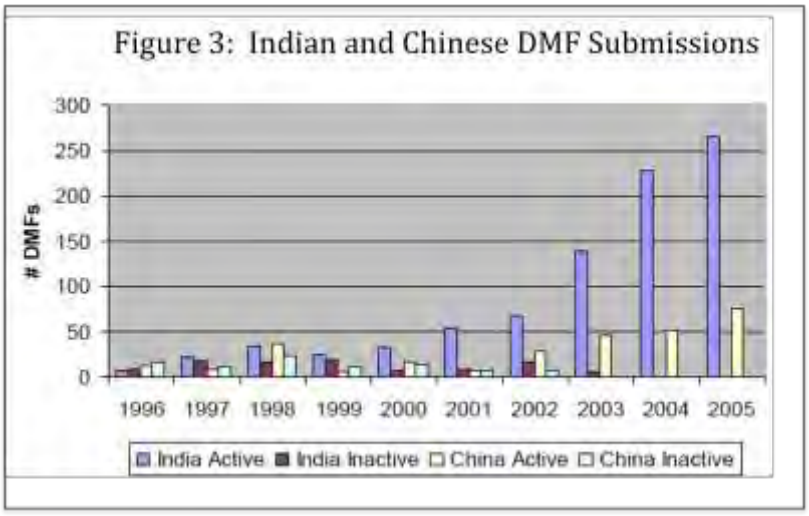
In the second case, an international producer from e.g., China manufactures an API and sells it to a final formulator in e.g., the United States. The API will be subject to the regulatory authorities in China and the API manufacturer will have to produce it, at a minimum, with the quality standards enforced by the Chinese authorities. However, the US can require that for importation, it meets USFDA standards as well.

The USFDA uses Drug Master Files (DMFs) to regulate APIs by stipulating that a final formulator manufacturing according to USFDA guidelines can only buy APIs from firms with an approved US Drug Master File (US-DMF). An API manufacturer submits a US-DMF to the USFDA with complete information on an API, including information on facilities, processes, and articles used in manufacturing. The USFDA, however, will not review the DMF until the final formulator files a New Drug Application (NDA), Abbreviated New Drug Application (ANDA) or ANDA supplement with the USFDA which requests use of this API in a finished formulation. Once a final formulator files, the USFDA schedules a Pre Approval Inspection of the API manufacturer and reviews the API manufacturer's DMF. If a final formulator does not file to use the API, the USFDA assigns the DMF a number when it receives the DMF but does not review it.[22] The USFDA does not approve DMFs, just ANDAs/NDAs that contain a DMF.

Case Study: USFDA issues warning letters to Ranbaxy Laboratories and an Import Alert for Drugs from two Ranbaxy plants in India citing manufacturing deficiencies. In September 2008, the USFDA issued warning letters to Indian manufacturer Ranbaxy as it was concerned about deviations from U.S. current Good Manufacturing Practice (cGMP). The Import Alert allows U.S. officials to detain any API and finished drug products manufactured at these facilities (over 30 different generic drugs) at the U.S. border. In addition, until Ranbaxy resolved the noted deficiencies and came into compliance with U.S. cGMP requirements, the USFDA recommended denial for any NDAs and ANDAs that list the cited Ranbaxy plants.[23]

Case Study: Baxter recalls heparin. In January and February 2008, Baxter, a US pharmaceutical firm which manufactures approximately 50% of the US heparin products, voluntarily recalled its heparin due to nearly 350 reported adverse events, including 19 deaths. Upon the initial recall, Baxter and the USFDA revealed that the recalled heparin products contained a contaminated API. The tainted API, imported from Changzhou SPL China, contained a heparin-like contaminant that was structurally similar to heparin and not recognized in the solution until the FDA developed special testing for it. In March 2008, the FDA announced that they had identified the contaminant to be an altered form of an oversulfated chondroitin sulfate which is not a natural byproduct of the heparin manufacturing process.[24] In April 2008, the US government held hearings[25] and determined the cause to be non-sterile equipment, lack of following proper procedures, and lack of expertise.[26]

To have an API appear in a drug marketed in Europe, API manufactures need to submit an EDMF (European Drug Master File). API manufacturers also pursue DMFs as the market views them as a sign of quality and they can boost global sales. Figure 3[27], below shows DMF submissions by Indian and Chinese API manufacturers in recent years and illustrates the recent and stark boom in Indian API manufacture.



If Nigeria imports an API from China, then NAFDAC will determine whether they will accept the Chinese approval of the API or require a different standard. Many developing countries do not have the resources to start inspections in foreign countries. The USFDA categorizes regulatory agencies in three categories: well-resourced, under-resourced, and no-resourced (ratings are confidential).[28] The USFDA, for example, is considered well-resourced with an approximately $2B annual budget. Furthermore, with their cost-conscious markets, African countries often do not have the political will / economic resources to follow the USFDA standards. Oftentimes, therefore, governments accept the Chinese standards. However, firms in Nigeria can always, at the manufacturers' discretion, pursue SRA approvals and use this as a sign of quality to help win business (if consumers are willing to pay for quality) in either local Nigerian markets or export markets.

Case Study: China executes top food and drug regulator for taking bribes to approve untested medicine. In July 2007, Beijing's No. 1 Intermediate People's Court convicted Zheng Xiaoyu of taking bribes in cash and gifts worth more than 6.49 million yuan (US$832,000) while he was director of the State Food and Drug Administration. Those bribes allowed eight companies to circumvent drug approval standards — including an antibiotic blamed for at least 10 deaths.[29]

Yan Jiangying, deputy policy director of the State Food and Drug Administration said, "As a developing country, China's current food and drug safety situation is not very satisfactory because supervision of food and drug safety started late. Its foundation is weak, so the supervision of food and

drug safety is not easy."[30]

The fourth case involves drugs financed by an international body. For example, if the government of Nigeria purchases HIV/AIDS drugs paid for with money from The Global Fund, The Global Fund will insist that WHO Prequalification (PQ) or an SRA is involved in the drug regulation. Or if the NGO Médecins Sans Frontières (MSF) purchases drugs for use by MSF teams working in a country, MSF will use its own quality control procedure based on WHO Good Manufacturing Practices (GMP) compliance. MSF uses its own inspectors to conduct GMP audits yet also takes into consideration outcomes of WHO PQ, ICH inspections or PIC/S.[31]

WHO Pre-Qualification

The World Health Organization started its PQ program in 2001 to ensure that final formulations purchased with UN monies would be of acceptable quality. Only firms that have passed a WHO PQ assessment can bid on UN tenders. WHO, NGOs, and national regulatory authorities use GMP standards to assess manufacturers; the difference is often in the stringency with which the regulatory authorities apply GMP standards. As a result, WHO PQ of a final formulator is an indicator to the market of quality.

Traditionally, WHO PQ just applied to final formulations. Part of the PQ process required final formulators to use GMP procedures to acquire APIs. This theoretically ensures a quality API. However, in the late 1990s, WHO became more concerned about the quality of APIs, especially following an incident in 1995 and 1996 when more than 100 children died in Haiti following ingestion of cough-and-cold syrup containing a counterfeit excipient: a Chinese chemical company sold diethylene glycol labeled as glycerin to the cough syrup manufacturer. The WHO Expert Committee on Specifications for Pharmaceutical Preparations responded by identifying several activities to control and ensure safe trade of starting materials for pharmaceutical products. In May 1999, The World Health Assembly adopted the Revised Drug Strategy resolution (WHA52.19) which requested WHO to prepare a new WHO Scheme for the Certification of Pharmaceutical Starting Materials Moving in International Commerce, which WHO released in 2001.[32]

The WHO Expert Committee on Specifications for Pharmaceutical Preparations discussed the need for WHO PQ of APIs at its fortieth and forty first meetings (October 2005 and 2006, respectively). The WHO PQ Program then drafted an API PQ procedure, which the Expert Committee endorsed in principle at its forty second meeting (October 2007), and adopted at its forty-third meeting (October 2008), subject to approval by WHO Legal Counsel.[33]

While the procedures for WHO API PQ have been approved, WHO does not currently have the resources to implement them. WHO is currently gathering donor support for API PQ. The first wave of APIs will be for priority essential medicines, neglected diseases, antimalarials, and TB drugs. Drugs like paracetamol (which are easy to

manufacture and have many API sources) and drugs for chronic diseases will not be as high a priority.[34]

WHO is also gathering donor support for an initiative to harmonize regulatory agencies across regional blocks in Africa[c] and an initiative regarding the quality of drugs for neglected diseases, a category often hampered because these drugs are not a high priority for developing country regulatory bodies and not much is known about them.[35]

The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use

The regulatory authorities of the US, Europe, and Japan along with research-based industry representatives have come together under the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) to reduce duplicate testing and coordinate technical guidelines and requirements for product registration. ICH guidelines have been adopted as law in several countries, but are only used as guidance for the USFDA. In 1998, the ICH released Q7: Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients. Table 3,[36] below, shows what stages the Q7 guidelines are used in the pharmaceutical manufacturing process.

Table 3: Application of Q7 to API Manufacturing

Type of Manufacturing	Application of Q7 to steps (shown in grey) used in this type of manufacturing					
Chemical Manufacturing	Production of the API Starting Material	Introduction of the API Starting Material into process	Production of Intermediate(s)	Isolation and purification	Physical processing, & packaging
API derived from plant or animal sources	Collection of organ, fluid, tissue, or plants	Cutting, mixing, and/or initial processing / extractions	Introduction of the API Starting Material into process	Isolation and purification	Physical processing, & packaging
Herbal extracts used as API	Collection of plants		Cutting and initial extraction	Further extraction	Physical processing, & packaging
Biotechnology: fermentation/ cell culture	Establishment of master & working cell bank	Maintenance of working cell bank	Cell culture and/or fermentation	Isolation and purification	Physical processing, & packaging
"Classical" fermentation to produce an API	Establishment of cell bank	Maintenance of the cell bank	Introduction of the cells into fermentation	Isolation and purification	Physical processing, & packaging

[c] There are six regional blocks in Africa: the Southern African Development Community (SADC), East African Community (EAC), Common Market for Eastern and Southern Africa (COMESA), Economic Community of West African States (ECOWAS), Economic Community of Central African States (ECCAS), and the Intergovernmental Authority on Development (IGAD). Countries can belong to multiple blocks.

The Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme

The Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (jointly referred to as PIC/S) includes Argentina, Australia, Canada, Iceland, Israel, Liechtenstein, Malaysia, Norway, Singapore, South Africa, Switzerland and the countries of the European Union (except Bulgaria, Latvia, Luxembourg and Slovenia).[37] Historically, The Global Fund also considered PIC/S members as SRAs, but eliminated this option as of July 1, 2009.[38]

The African Final Formulations Pharmaceutical Market

In 2006, The IFC estimated the Sub-Saharan Africa pharmaceutical market to be worth $3.8 billion. Local final formulators created 25-30% of this value, or approximately $1B. While 37 Sub-Saharan African countries have some pharmaceutical production, South Africa dominated the sector with over 70% of the region's annual pharmaceutical production. Nigeria, Kenya, and Ghana together represent another 20%. Nigeria and Ghana focus more on local consumption whereas Kenya exports 35-40% of manufacturer's sales. [39] Figure 4[40] provides more detail:

Figure 4: Estimated Pharmaceutical Market in Sub-Saharan Africa

The sector is also growing: The IFC estimated that 40% of the cumulative $1.6-$2.9B projected investment in health care in the region between 2007 and 2016 will be invested in generic final formulation manufacturing. And the Sub-Saharan African governments and regional bodies support developing Africa's production. For example, the African Union's 2007– 2015 health strategy stated that "African Union Member States need to embark on local production of pharmaceuticals and

other health commodities." [41]

Most sub-Saharan African final formulation manufacturers, outside of South Africa, manufacture non-complex, high volume, essential products, such as basic analgesics, simple antibiotics, anti-malarial drugs, and vitamins.[42] This can be attributed to the following factors:

- ***Demand for more expensive drugs is not fully developed.*** While many African manufacturers could make higher end products, consumers may not purchase them.[43] In these markets, many consumers are extremely price-conscious. Furthermore, the African markets for antihypertensives and antidiabetics are unregulated and fragmented with each country procuring from local manufacturers. Market intelligence for these small markets can be scarce, making it difficult for a manufacturer to pursue a market.[44] Further research is required, however, to determine the degree of importance of these variables.
- ***Cheaper drugs have lower working capital requirement.*** The price of an API may deter small final formulators. Oftentimes these firms are relatively new and have small capital bases. The six month lag between purchasing an API and then selling the subsequent final formulation requires a working capital investment. Therefore, firms may be attracted more to drugs where the API cost is relatively small compared with more complex drugs where the APIs can costs thousands of dollars per kilo. However, this capital investment may not be so large as to be insurmountable.
- ***Over the Counter (OTC) branded drugs have higher profit potential.*** Many manufacturers of OTC drugs brand their drugs and enjoy high margins with good marketing. Other drugs, such as many antibiotics, require physicians to inject it. As the patient may not even know the brand, the manufacturer cannot position these prescription drugs with a high price. As a result, most generic final formulators have branded generics such as paracetamol in an attempt for their version to be perceived as a higher quality option, and hence a higher priced drug. For example, in Bangladesh, various brands of ciprofloxacin range from $0.07 to $0.20 per unit but various dexamethasone eye drops range from $0.34 to $1.29 per 5ml.[45]

A large question for the public health community therefore is where these final formulators are procuring APIs and how quality is ensured. Oftentimes, Sub-Saharan African final formulators procure unregulated APIs from India and China. For example, one Ghanaian final formulator estimated that less than 30% of the APIs imported from India and China to Ghana come from facilities with WHO GMP or SRA approval.[46] African final formulators tend to procure unregulated APIs for two reasons:

- ***Cost-sensitive under-regulated markets:*** In most sub-Saharan African countries, with the notable exception of South Africa final formulator firms operate in a looser regulatory environment where WHO GMP or SRA approvals

are not required. Local final formulation firms in these countries can produce pharmaceuticals according to the less stringent local requirements or self-select to get these certifications. However, if they are not required, the incremental costs of obtaining these certifications can price them out of the local market. The increased costs attributable to:

- ***Manufacturing costs:*** Manufacturers often have to make costly improvements to facilities to bring them and keep them to WHO GMP or SRA levels, often including renovation of production facilities, familiarity with qualification requirements and processes, and a dossier of product efficacy and safety tests that meets with regulatory bodies' requirements. Furthermore, the costs of obtaining WHO GMP or SRA approvals are relatively higher for firms with small volumes.
- ***Increased API costs:*** APIs from certified facilities can command a 20-100% price premium. This premium gap, however, is product dependent (more steps usually result in a higher premium)[47] and is shrinking as more suppliers achieve certification.[48] In cost-sensitive markets, the average consumer is often unwilling to pay a premium.
- ***Supply chain rigidity:*** A final formulator working with WHO GMP or SRA approved procedures usually will only have a few approved API manufacturers to supply it (adding a new API supplier requires about six months, is costly, and requires updates to regulatory authorities). Therefore, a final formulator might not shift API suppliers easily. As a result, some final formulators may not be able or willing to switch if, for example, another firm offers the API for 5% less[49] or they may have difficulties finding a particular API if the API market moves quickly. Larger final formulation firms, however, usually have the volume and relationships to be able to secure APIs.[50] Appendix Four details recent API price volatility.

- ***Lack of technical knowledge:*** Many newer, smaller African final formulators do not have the technical knowledge to successfully maneuver the international API markets.

Two challenges for APIs in Developing Countries:

In general, the global API market is an efficient market based on commodities. However, two potential challenges may impede equality of access to quality APIs for small final formulators in developing countries.

1. ***Transparency:*** Small local final formulating firms procuring APIs on the global merchant market, usually from API-manufacturing firms located in either India or China, can find that navigating the market is challenging, especially when procuring non-WHO GMP or SRA approved APIs. Furthermore, as historically, Chinese API manufacturers could not directly export but had to go through a state-owned trading company, many Chinese API manufacturers still use such trading companies.[51] As a result, some firms may use a trader or merchant intermediary

such as Helm AG, Indukern Chemie AG, or GMP Pharma Trading AG, to source APIs. Unfortunately, these traders were not interested in being interviewed for this exploratory study, which implies a tendency towards non-transparency. It would add value to the discussion of quality APIs, however, to continue to attempt to include the point of view of these traders.

For example, when F. Hoffmann-La Roche Ltd. procure APIs on the global merchant market, they use USFDA audits along with internal F. Hoffmann-La Roche Ltd. audits focusing on the supply chain, facilities, and technical processes to validate the quality of an API manufacturer directly. F. Hoffmann-La Roche Ltd. prefer to work directly with the manufacturer as direct contact with a manufacturer affords more transparency to the supply chain. A manufacturer will always know the process better, be able to do necessary quality control checks directly, and has an appointed quality person on staff who can provide any requested certification.[52]

Many smaller final formulators without the resources and experience of F. Hoffmann-La Roche Ltd. may find it appealing to rely on a trader to source APIs. If so, the final formulator should evaluate both the supplier and the channel.

2. Ensuring API manufacturers stay in the market: When API manufacturers no longer view the API market worth competing in, they may leave the market, and then final formulators may not be able to find the low-cost, high-quality API they used to procure. Possible causes for API manufacturers to leave a market include:

- ***Market price moves too low:*** API manufacturers are finding their margins squeezed and are under tremendous pressure to produce more for less or leave the market. Final formulators continuously push for lower API prices as they face incredible price competition themselves, to the point of sometime focusing more on market share than on profitability.[53] At the same time, raw material prices and environmental costs are rising. For example, Piramel Healthcare in India recently left the ibuprofen API market as they could not compete;[54] three producers in China now manufacture it.[55]

  However, the normal laws of supply and demand dictate that, excluding other factors, APIs priced too low should rise, and, once it reaches profitable levels again, API manufacturers will re-enter the space. This dynamic is often observed within the antibiotics market in China.[56]

  Each API market, however, is not just one market but two: some manufacturers targeting regulated markets with approved facilities and higher cost APIs and other manufacturers targeting unregulated markets with fewer quality mechanisms put in place (and sometimes the same manufacturer may operate in the two markets with two separate plants). Final formulators, often under incredible price pressures, and are more and more willing to take risks with less established companies. These decisions impact the API market. Usually within a

market segment, higher quality manufacturers exit first, leaving the market to monopolists or lower quality manufacturers.[57]

- ***Small markets:*** API manufacturers may be hesitant to dedicate capacity to a small or declining market. In general, an API manufacturer would not be interested in a small / declining market if either all of its capacity was fully utilized for other products (and the manufacturer determined it was not wise to build more capacity at that moment) or if the manufacturing of the required API could not easily fit it into its production schedule (e.g. the API requires larger than normal changeover of production lines or a different technology). As such, some neglected disease APIs and small market APIs still get overlooked. For example:
    - Chinese firms, with their heritage as SOEs (State Owned Enterprises) are driven by large volumes and often not interested in smaller niche markets, unless it is a high value product.[58]
    - If a small volume final formulator is committed to a single API manufacturer due to regulatory filing requirements, then the final formulator may face an abrupt and unreconcilable discontinuation of APIs when the API manufacturer leaves the field.[59]
    - If the API demand volume is very small, many API manufacturers will not be interested due to change-over times and higher costs associated with smaller scale production. The final formulator, in this case, will still be able to find the API, but the cost may be prohibitive. [60]

      Case Study: Aventis re-enters eflornithine market: Aventis, a French pharmaceutical firm, manufactured eflornithine to treat trypanosomiasis (sleeping sickness), a disease which affected approximately 500,000 people in 36 African countries. Aventis halted its production in 1999 because it did not consider it a profitable drug. In 2001, after Médecins Sans Frontières petitioned WHO to take a position, Aventis resumed production and agreed to donate $5M worth of eflornithine per year for five years. Aventis agreed that after those first five years, they would start a technology transfer with technical assistance to any capable manufacturer willing to continue production on their own. By September 2005, WHO identified two manufacturers (one in India and one in Texas), both of which were investigating inexpensive ways of producing eflornithine. Treating trypanosomiasis received a huge boon when eflornithine was also shown to be an effective facial hair growth inhibiting agent, with a large potential market among women in developed countries. The development of the hair removal market partly encouraged Aventis to re-start the manufacture of eflornithine and allowed it to once again become available for use in trypanosomiasis .[61]

- ***Economies of scale:*** These economies of scale function relative to the market size – one market may be only large enough to sustain one manufacturer while

another market could sustain hundreds. Once an API manufacturer has achieved a significant economy of scale on a small market, it often does not make sense for any other manufacturer to enter. As a result, the scaled manufacturers can become monopolists and charge higher prices. However, these higher prices could draw new competitors into the market, unless the API firm can prevent it by taking advantage of its size to control the raw materials or some other aspect of the market.

There are a couple of reasons why normal economies of scale rules do not always apply to APIs, such as:

- Chinese firms often lack commercial sophistication and market intelligence; they are also opaque in their own transactions. Therefore if it is anticipated that a product will sell in high volumes, new entrants will quickly scale-up to become the largest in an attempt to drive everyone else out of the market without knowing what other firms are doing. This can result in over-production for many products.[62]
- Lower quality manufacturers can force higher quality manufacturers out of the market by entering a space on an aggressive scale while cutting some quality corners.

Recommendations:

The following should be maintained as a public health goal: A sustainable and competitive high quality API market that developing country final formulators can access for all essential drugs. This requires looking at the market with an eye towards sustainability, quality and price. In order to accomplish this, the following actions are recommended:

Recommendations for Global Partners

1. ***Train Sub-Saharan African Final Formulators:*** Global partners should help train final formulators in developing countries to assess API quality and the best way to demand / obtain higher quality APIs. Just like Western buyers, African buyers must do their due diligence when procuring APIs. African final formulators should have a solid quality assurance system, understand requirements, and institute written SOPs so that they are able to maintain appropriate quality standards and environmental requirements.[63]

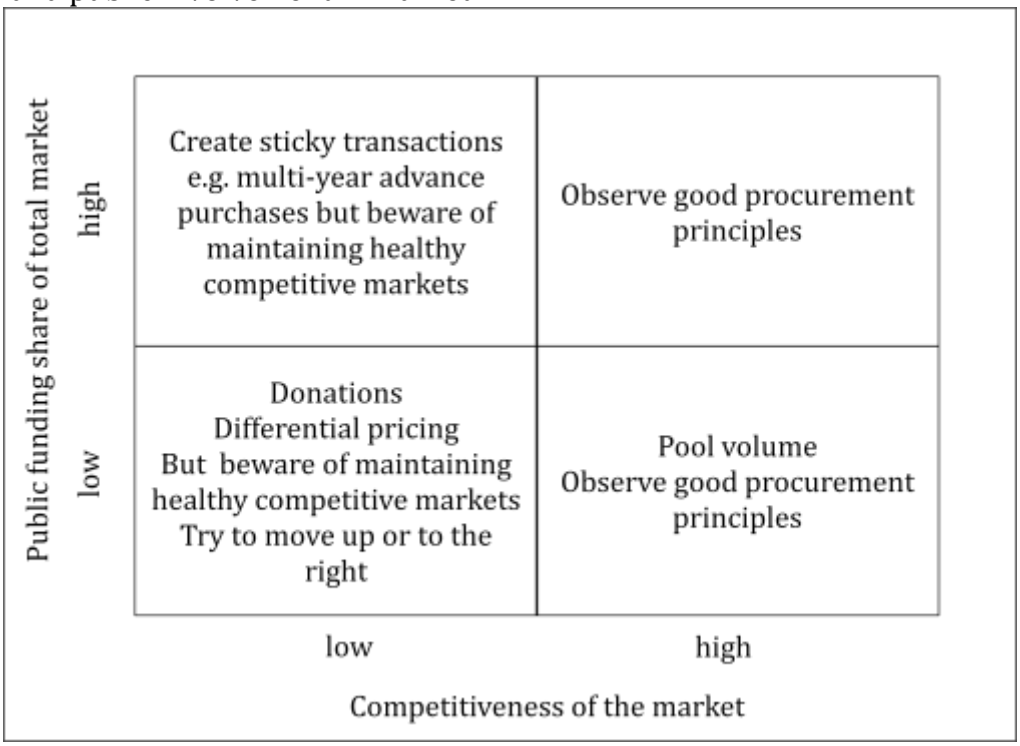
2. ***Raise API regulatory capacity:*** Increased regulatory capacity and stringency helps everyone: the public benefits through greater drug safety; the manufacturers benefit as it makes them more internationally competitive.
   - ***API producing countries:*** Global partners should work with the regulatory agencies in China and India to ensure regular contact with international agencies (such as the WHO) and SRAs (such as the USFDA) in order to increase their regulatory capacity.

- ***Developing countries:*** Increased regulatory stringency in these countries will deter manufacturers facing cost sensitive markets to meet demand by supplying low quality APIs. However, increased regulatory stringency is not just an issue of training and capacity building, but it is also increased political will. Specific areas to consider include:[64]
  - National and regional legislation on medicinal products should be extended to cover starting materials.
  - Key parties in the chain – producers, traders, forwarders, tenderers, brokers – must be authorized for their activities by the competent health authority of the country in which each activity occurs.
  - Strengthening GMP capacity to inspect.

3. ***Work for healthy, sustainable, competitive API markets when procuring:*** Sometimes pricing and commodity security can be in conflict. Low prices are often achieved through single-firm contracting (to get scale) and negotiating reduced short-term prices. Commodity security can be achieved through the existence of multiple manufacturers that provide a secure supply of existing products, pricing schemes which provide space for manufacturers to invest in R&D for future products, and development and maintenance of competitive markets.

   The approach to each API should be specific to its intended final formulations and market characteristics. If an API market already has product competition, better access could be encouraged through price reductions via purchaser leverage, e.g. bulk-purchasing. The Global Drug Facility for first-line TB drugs is a good example of an international effort in this area. If an API market only has limited suppliers, commodity security could be encouraged via advance purchase firm contracting and tailoring contract terms and length so as to encourage a longer-term competitive environment. The Global Alliance for Vaccines and Immunization (GAVI) and the Green Light Committee (GLC) for multi-drug resistant tuberculosis (MDR TB) are examples.[65] Figure 5[66], below, illustrates a potential framework that could be used to identify appropriate interventions.

Figure 5: Appropriate international responses based on market competitiveness and public involvement in market.



Appendix Five details more information on the competitiveness of some specific drugs/APIs and international responses to these product situations, but more research is required in this area.

There are many ways to impact individual API markets. Below is a list of options though further study is required to determine which mechanism would be most appropriate for which API.[67] In general, procurement procedures that foster competition / lower pricing through the basic principles of transparency, quality, and sustainable markets with multiple manufacturers should be utilized. Also, existing mechanisms should be optimized rather than creating duplicate channels.

- Pooled demand: the fewer the buyers and the larger the percentage of their respective market shares in terms of value, the greater their influence in negotiating prices with producers. A less fragmented purchasing base can also make the market more predictable, and predictability is conducive to more cost-efficient manufacturing, the savings of which may be passed onto buyers. Clearer demand can also create incentives for additional suppliers to enter the market.
- Bulk purchasing: less sophisticated than, but similar to, pooled demand.
- Competitive tendering that allocates shares to multiple manufacturers.
- Long-term agreements.
- Providing product financing or guaranteeing financing.
- Offering professionally managed procurement services.

- Helping to reduce risk when selling to Africa: Some Chinese and Indian firms may be concerned about payment terms and the ability to pay in Africa. This risk results in higher prices and hesitation to sell.[68]
- Signaling predictable demand to manufacturers to incentivize them to enter / stay in the market.

Regardless of the mechanism chosen, supply and demand changes in the market should be monitored in order to determine whether the market remains healthy enough for multiple suppliers to enter into and maintain manufacturing capacity.

A concrete process goal could be to identify approximately twenty critical APIs and then identify a sustainable number of suppliers for each. While further work is required to identify potential mechanisms, the global partners should then make a concerted effort to work with these suppliers to encourage them to stay in the market.

4. ***Increase market transparency:*** API markets are often fragmented and undocumented, creating additional risk and cost for manufacturers. Identifying who manufactures which final formulations on the ground in developing countries is challenging. finding information regarding who manufactures the APIs behind these final formulations is even more difficult. Many regulatory documents keep APIs confidential. No public database exists that tracks API manufacturers and quality assessments. And while many organizations will show up at trade shows, final formulators may still find it challenging to sift through the market to find a good API manufacturer.[69] The following actionable items would improve market transparency:

   - Better demand forecasting
     - Predictable forecasting makes a market more attractive to manufacturers.
     - Demand may increase with better forecasting as countries better understand epidemiological need.
   - Collecting and disseminating transparent pricing & quality information which allows purchasers to compare suppliers.
   - Compiling and sharing country experiences and best practices in policy change, procurement, financing, subsidies and delivery.

   While an all-inclusive registry would be an enormous task and potentially futile in fast-moving markets, global partners should join hands to start a global repository for information on manufacturers, the products they make, and their regulatory approvals. Many international agencies have started such a list for products in their area of work, but it has yet to be collated and made public.[70]

5. ***Investigate WHO activities in API quality:*** WHO is gathering donor support for several initiatives which could increase API quality and access. These initiatives

deserve further investigation to see if a partnership approach or support would be appropriate.

Recommendations for drug manufacturers/final formulators

6. ***Gain regulatory approvals:*** Small manufacturers could improve their public image through increasing their quality assurance measures. Producing APIs without some form of regulatory approval is a dangerous public health threat. Firms could consider (in increasing levels of stringency) self-assessments, WHO GMP, WHO PQ, PIC/s approval, or SRA approval.

7. ***Learn API procurement skills:*** Just as final formulators from developed countries have trained procurement staff who understand the global API market, final formulators in developing countries should have staff that can understand and manage their engagement in the global API market.

8. ***Acquire testing facilities:*** All final formulators must have access to suitably equipped analytical testing laboratories in order to control incoming materials and final products.[71]

Appendix One: List of Interviewees

Global Pharmaceutical Manufacturers

- F. Hoffmann-La Roche Ltd. Juergen Knoebel.

Indian API Manufacturers

- Aurobindo. Ramaprasada Reddy, CEO.
- Cipla. Amar Lulla. Joint Managing Director and Director.
- Dr. Reddy's.
- Hetero Drugs. Mr. Narsa Reddy, Director.
- IPCA. Premchand Godha. Managing Director.
- Nicholas Piramel. Nandina Piramel. Executive Director.

Pharmaceutical Associations

- Bulk Drug Manufacturers Association (India).
- Indian Pharmaceutical Association. Dilip Shah. Secretary General.
- PhRMA. Mark Paxton. Associate VP, International Regulatory Affairs.

US Government

- US Department of Commerce. Vince Suneja. Director, Pharmaceuticals and Medical Devices.
- USFDA Center for Drug Evaluation and Research (CDER). Justina Molzon. Associate Director for International Affairs.

NGOs, Universities, International Organizations and Consultancies

- Clinton Foundation. David Ripin. Scientific Director, Drug Access Program.
- HLSP. Cheri Grace. Lead Specialist, Access to Medicines.
- Howard University. Joseph Fortunak.
- PharmaVantage. Susan Capie. CEO.
- Research Institute for Industrial Pharmacy, South Africa. Theo Dekker.
- Thomson Reuters. Kate Kuhrt. Director, Generics and API Intelligence. Healthcare & Science.
- World Health Organization. Dr. Lembit Rago. WHO Coordinator of Quality Assurance and Safety for Medicines.

Appendix Two: China

China has a large and vibrant pharmaceutical sector. In 2007, the Chinese pharmaceutical market, excluding traditional Chinese medicines, was $ 15.6 billion, or 2% of the global market. The API market in 2005 was nearly $5.7B[72] and it has been growing rapidly at 15-19% per annum. China has 4,682 API and final formulator manufacturers,[73] 3,101 of which are certified GMP (Good Manufacturing Practices) by the SFDA (the State Food and Drug Administration). Ninety-seven percent of products are generic copies, and 70% are made by local manufacturers.[74]

Although the Chinese marketplace is rapidly evolving and highly diverse, Chinese firms tend to work more with raw materials, intermediates and APIs. Chinese firms are very strong in fermentation. APIs account for 84% of China's pharmaceutical exports.[75] Chinese firms produce 1,500 APIs, with a volume of about 732,000 metric tons.[76]

The Chinese API industry is small-scale and fragmented even though each of the top 20 exported APIs has more than 50% global market share. For example, in 2006, only two manufacturers were among the top 500 national Chinese enterprises and pharmaceutical firm sales were less than 25% of the average sales of the top 500 Chinese companies and less than 1% of Pfizer's sales. While the top 10 global pharmaceutical firms contributed 44% of the global sales in 2006, the top 10 Chinese pharmaceutical firms contributed only 14% of China sales in 2006. [77]

However, the industry is rapidly consolidating. For example, the number of API manufacturers has decreased by 50% since 1999[78] due to industry consolidation and firms leaving as they were unable to meet increasingly strict quality and environmental standards.

Chinese firms are rapidly advancing but still need to overcome the following barriers to play a larger role in the global economy:

- ***Technical skills:*** Skills and standards among Chinese manufacturers vary widely. Some Chinese firms' plants, equipment, and skills rival Western companies while others lag. While the chemistry being handled becomes more sophisticated each year, [79] on average, China still lags behind global standards in complexity of products manufactured. For example, in China, the API to Final Formulation price ratio is 1:3. In India it is 1:5.2 and in developed countries it is 1:10. [80]

- ***Transition to market economy:*** Chinese firms continue to move away from the traditional SOE (state-owned enterprise) focus on volume sales towards private firms focused on profit. In 2006, 36% of the firms were government owned, 35% privately owned and 29% foreign-funded.[81] This transition provides challenges for production decisions. In the past, a planned economy meant the

government dictated what factories produced and where their products were sold, and subsidized operations. But as the economy shifts to a market economy, subsidies have been reduced or withdrawn, leaving manufacturers responsible for portfolio management and production decisions.[82] Without accurate market information or a culture of making production decisions based on market realities, firms often duplicate production. For example, in a consolidating market, the SFDA has approved 1,600 generics in 2002, 6,100 in 2003, and more than 8,000 in 2004/5. For levofloxacin hydrochloride injection, there were 145 approvals alone.[83]

- ***Transparency:*** Historically, manufacturers could not directly export products but had to work with a state owned trading company. Now manufacturers can sell directly on the international market, but many still prefer to work with a trading company. Because of this, buyers often have a hard time seeing all the way up the chain to the manufacturer in order to evaluate it.[84]

- ***Regulatory stringency:*** The SFDA is becoming increasingly stringent and forcing low quality manufacturers out of the market. The SFDA is based on the USFDA (United States Food and Drug Administration)[85] and continues its cooperation with the US. For example, in December 2007, the SFDA and USFDA signed an agreement to strengthen cooperation between the U.S. Department of Health and Human Services and the SFDA, to establish three USFDA satellite outposts in China, and to have SFDA agents accompany their FDA counterparts during GMP inspections in China.[86]

  However, gaps still exists. SFDA officials acknowledge that responsibility for food and drug safety involves as many as 17 government agencies, ranging from the Ministry of Health, which sets hygienic standards, to the Public Security Bureau, which has the power to investigate criminal cases. This fragmented authority has created overlapping jurisdictions in which no single agency exercises ultimate responsibility.[87]

  Also, chemical companies that make products as diverse as fertilizers and industrial solvents are neither certified nor inspected by Chinese drug regulators, yet export chemical intermediaries for pharmaceuticals. The New York Times interviewed Wang Siqing, managing director of the Changzhou Yabang Pharmaceutical Company in 2007. Mr. Siqing estimated that uncertified chemical companies make half the active pharmaceutical ingredients sold in China. The New York Times identified at least 1,300 Chinese chemical companies advertising compounds destined for pharmaceuticals on internet trading sites. And the results can be devastating. In the mid-1990s, a Chinese chemical company sold diethylene glycol labeled as glycerin to a cough syrup manufacturer. This resulted in nearly 100 child deaths in Haiti. In 2006, at least 138 Panamanians died or were disabled after another Chinese chemical company sold the same poisonous ingredient mixed into cold medicine.[88]

- ***Environmental regulation.*** China has historically been criticized for lax environmental protection. For example, a November 2003 New York Times article entitled "Toxins Are Part of Cost of Boom in China's Exports" documented major violations of toxic waste regulations at Zhejiang Hisun, an FDA-approved manufacturer in Taizhou, which resulted in the death of employees and illness among the local population.[89] Increasingly, China is toughening environmental protection.

- ***Communication:*** Language continues to be a barrier.[90]

- ***Intellectual Property (IP):*** Although Chinese companies are becoming better informed about intellectual property issues and expectations, most Chinese firms do not have a legal staff devoted to patent searches.[91] There appears to be little understanding of the official IP policy and IP enforcement is weak. While China's central government has largely followed through on its WTO (World Trade Organization) IP commitments, the local levels often lack the will and ability to enforce the policy.[92]

- ***Counterfeits:*** China has a thriving counterfeit medicine industry--a big headache for western drug makers and public health authorities around the world.[93] In the second half of 2008, the SFDA launched an electronic tracking network pilot program. Starting in 2009, all pharmaceuticals and biologics sold in China will eventually be marked with its barcode tags. The new tracking system will lay the groundwork for a rapid response to any adverse events triggered by drugs or devices and help crack down on poorly made or counterfeit products.[94]

Appendix Three: India

The Indian pharmaceutical industry is a vibrant, rapidly growing and evolving industry with both APIs and final formulations.

While Chinese firms historically tended to manufacture high volume, low complexity APIs such as paracetamol, Indian firms tended to focus on lower volume, more complex APIs.[95] (The paracetamol market has consolidated to three producers in China with large economies of scale.[96]) The ferocious competition between the two countries continues and, over the last few years, as the Indian industry has not been able to keep pace with the Chinese prices and as the Chinese continue to catch up in technology skills, several Indian firms have shut down some business lines, let the business go to Chinese firms and then moved on to more complex products.[97]

Indian API manufacturers have also been investing and acquiring firms in China.[98] For example, Matrix Laboratories in India (which is currently being wholly taken over by Mylan Pharmaceuticals in the US) recently took a 60% stake in Mchem Group, a China-based manufacturer of chemicals, intermediates and APIs.[99] Dishman Pharmaceuticals & Chemicals, another Indian firm has an office in Wuxi that both sources and looks for opportunities to partner with Chinese manufacturing organizations.[100] In 2006, Dishman also planned to invest $10M to build an API manufacturing facility near Shanghai.[101]

Tables 4, 5, 6, and 7, below[102], give detailed data on Indian firms sales, exports, and imports.

Table Four: Growth in Indian API Industry

(Rs. in crores)

Year	Bulk Drugs	Growth (%)	Formulations	Growth(%)
1985-86	416.00	10.3	1945	6.5
1986-87	458.00	10.2	2140	10.0
1987-88	480.00	4.6	2350	9.8
1988-89	550.00	14.6	3150	12.5
1989-90	640.00	16.4	3420	8.6
1990-91	730.00	14.1	3840	12.3
1991-92	900.00	23.3	4800	25.0
1992-93	1150.00	27.8	6000	25.0
1993-94	1320.00	14.8	6900	15.0
1994-95	1518.00	15.0	7935	15.0
1995-96	1822.00	20.00	9125	15.0
1996-97	2186.00	20.00	10494	15.0
1997-98	2623.00	20.00	12068	15.0
1998-99	3148.00	20.00	13878	15.0
1999-00	3777.00	20.00	15960	15.0
2000-01	4533.00	20.00	18354	15.0
2001-02	5439.00	20.00	21104	15.0
2002-03	6529.00	20.00	24185	15.0
2003-04	7729.00	20.00	27692	15.0
2004-05	9034.00	20.00	31946	15.0

* These figures do not include production from unorganized sector, which is estimated at an additional 35% of the production.

Table Five: Indian Firm Exports

Rs. In crores)

Year	Bulk Drugs	Formulations	Total
1985-86	33.36	106.59	139.95
1986-87	87.16	102.12	189.28
1987-88	139.71	88.25	227.96
1988-89	242.87	157.29	400.16
1989-90	350.50	314.20	664.70
1990-91	413.40	371.40	784.80
1991-92	722.60	558.50	1,281.10
1992-93	856.60	553.70	1,410.30
1993-94	1,009.60	771.80	1,781.40
1994-95	1,260.70	924.00	2,184.70
1995-96	1,132.90	2,044.80	3,177.70
1996-97	1,664.50	2,414.80	4,079.30
1997-98	2,214.80	2,926.80	5,141.60
1998-99	2,870.40	3,101.40	5,971.80
1999-00	3,100.00	3,752.00	6,852.00
2000-01	3,720.00	4,502.40	8,222.40
2001-02	4,501.00	5,447.50	9,948.50
2002-03	5,401.00	6,536.40	11,937.40
2003-04	6,481.00	7,843.20	14,324.20
2004-05	-	-	16,681.00

Table Six: Indian Firm Imports

(Rs. In crores)

Year	Bulk Drugs	Formulations	Intermediates, Chemicals Solvents & Others	Total
1985-86	208.13	15.82	43.44	223.95
1986-87	207.49	21.84	58.26	229.33
1987-88	234.13	21.44	93.87	255.57
1988-89	328.35	35.43	83.13	363.78
1989-90	425.64	55.09	171.39	480.73
1990-91	322.57	84.94	196.49	407.51
1991-92	458.51	96.12	252.75	554.63
1992-93	508.39	119.51	509.48	627.90
1993-94	612.74	138.33	415.46	751.07
1994-95	811.43	173.02	384.27	984.45
1995-96	1,630.00	270.00	505.00	1,900.00
1996-97	1,705.00	345.00	555.50	2,050.00
1997-98	1,827.00	430.00	611.00	2,257.00
1998-99	1,918.00	540.00	670.00	2,458.00
1999-00	2,025.00	680.00	736.00	2,705.00
2000-01	2,265.00	715.00	808.00	2,980.00
2001-02	2,435.00	855.00	887.00	4,177.00
2002-03	2,617.00	1,012.00	973.00	4,602.00
2003-04*	2,813.00	1,204.00	1,068.00	5,085.00
2004-05*	3,024.00	1,433.00	1,173.00	5,630.00

Notified Prices of Bulk Drugs as Specified in First Schedule of DPCO, 1995

S. No.	Name of the Bulk Drug	Unit	Price (Rs)	SO No. of the Gazette	Date of Notification
1	AMODIAQUINE HCL	KG	981.00	281 (E)	31/03/1997
2	ASPIRIN	KG	134.00	1,135 (E)	15/10/2004
3	ANALGIN (METAMIZOLE)	KG	458.00	1,429 (E)	30/12/2004
4	AMINOPHYLLINE	KG	419.00	1,007 (E)	04/10/1999
5	BENZATHINE PENCILLINE G (PEN G)	KG	2,055.00	1,837 (E)	29/12/2005
5a	POTT. PENICILLINE G (1ST CRYSTAL)	BU	727.00	201 (E)	07/03/2001
5b	POTASSIUM PENICILLIN G	BU	1,106.00	805 (E)	20/08/2001
5c	POTASSIUM PENICILLIN V	BU	1,001.00	806 (E)	20/08/2001
5d	PROCAINE PENICILLIN G	BU	971.00	1,837 (E)	29/12/2005
5e	SODIUM PENICILLIN G	BU	824.00	1,837 (E)	29/12/2005
6	BETAMETHASONE ALCOHOL	GM	220.00	1,307 (E)	14/09/2005
6a	BETAMETHASONE VALERATE	GM	209.00	1,307 (E)	14/09/2005
6b	BETAMETHASONE SODIUM PHOSPHATE	GM	175.00	1,307 (E)	14/09/2005
7	CHLOROTETRACYCLINE HCL	KG	1,877.00	479 (E)	03/07/1997
7a	DIMETHYL CHLORO TETRACYCLINE HCL	KG	4,559.00	206 (E)	31/03/1999
7b	TETRACYCLINE HCL	KG	782.00	1,065 (E)	29/10/2001
8	CHLOROQUINE PHOSPHATE	KG	706.00	414 (E)	24/03/2005
8a	CHLOROQUINE SULPHATE	KG	1,692.00	915 (E)	18/12/1992
9	CLOXACILLIN SODIUM (ORAL GRADE)	KG	1,154.00	1,301 (E)	14/09/2005
9a	CLOXACILLIN SODIUM (STERILE)	KG	1,652.00	1,301 (E)	14/09/2005
23d	ERYTHROMYCIN ETHYL SUCCINATE	KG	2,892.00	844 (E)	15/06/2005
23e	ERYTHROMYCIN PROPIONATE	KG	2,318.00	844 (E)	15/06/2005
24	ETHYLESTRENOL	KG	80,465.00	564 (E)	06/08/1997
24a	LYNESTRENOL	KG	73,995.00	414 (E)	24/03/2005
25	FRUSEMIDE	KG	1,473.00	765 (E)	07/07/2003
26	FURAZOLIDONE	KG	417.00	564 (E)	06/08/1997
27	FRAMYCETIN SULPHATE	KG	13,732.00	564 (E)	06/08/1997
28	FAMOTIDINE	KG	1,673.00	770 (E)	07/07/2003
29	GRISEOFULVIN	KG	4,270.00	419 (E)	11/05/2001
30	GENTAMYCIN SULPHATE BASE	GM	12.74	605 (E)	03/07/1995
31	GLIPIZIDE	KG	31,584.00	921 (E)	13/08/2004
32	HYDROXYETHYL THEOPHYLLIN (HET)	KG	511.00	1,302 (E)	14/09/2005
32a	THEOPHYLLINE ETHINATE OF PIPERAZINE	KG	513.00	36 (E)	14/01/1992
32b	THEOPHYLLINE	KG	439.00	1,302 (E)	14/09/2005
33	HUMAN INSULIN	KG	3,331,261.00	1,306 (E)	14/09/2005
33a	INSULIN	MU	24,017.00	564 (E)	06/08/1997
34	IBUPROFEN	KG	370.00	414 (E)	24/03/2005
35	METRONIDAZOLE	KG	470.00	804 (E)	20/08/2001
35a	METRONIDAZOLE BENZOATE	KG	373.00	414 (E)	24/03/2005
36	METHYL DOPA	KG	4,205.00	564 (E)	06/08/1997
37	MEBHYDROLINE NAPADISYLATE	KG	1,268.00	120 (E)	10/02/1998
38	NAPROXEN	KG	1,864.00	845 (E)	15/06/2005
38a	NAPROXEN SODIUM	KG	1,916.00	845 (E)	15/06/2005
39	NALIDIXIC ACID	KG	1,623.00	843 (E)	15/06/2005
40	NORFLOXACIN	KG	860.00	846 (E)	15/06/2005
41	OXYTETRACYCLINE HCL	KG	1,097.00	414 (E)	24/03/2005
41a	OXYTETRACYCLINE AMPHOTERIC BASE	KG	1,553.00	414 (E)	24/03/2005
42	PREDNISOLONE	KG	56,503.00	414 (E)	24/03/2005
42a	PREDNISOLONE ACETATE	KG	31,921.00	414 (E)	24/03/2005
43	PHENIRAMINE MALEATE	KG	1,107.00	1,838 (E)	29/12/2005
44	PYRANTOL PAMOATE	KG	1,204.00	1,305 (E)	14/09/2005

9a	CLOXACILLIN SODIUM (STERILE)	KG	1,652.00	1,301 (E)	14/09/2005
10	CHLROPROPAMIDE	KG	306.00	754 (E)	29/08/1995
11	CEFADROXYL MONOHDYRATE	KG	2,303.00	413 (E)	24/03/2005
12	CIPROFLOXACIN HCL	KG	4,190.00	227 (E)	20/03/1997
13	CAPTOPRIL	KG	11,971.00	443 (E)	13/06/1997
14	CEFOTAXIME SODIUM (STERILE)	KG	8,632.00	414 (E)	24/03/2005
15	CARBAMEZAPINE	KG	3,080.00	414 (E)	24/03/2005
16	CEFAZOLINE SODIUM (STERILE)	KG	9,398.00	769 (E)	07/07/2003
17	DIIODOHYDROXY QUINOLINE (DIHQ)	KG	547.00	728 (E)	21/08/1995
17a	IODOCHLORO HYDROXY QUINOLINE (ICHQ)	KG	702.00	414 (E)	24/03/2005
18	DEXTRO-PROPOXY PHENE HCL	KG	3,846.00	414 (E)	24/03/2005
18a	DEXTRO-PROPOXY PHENE NAPSYLATE	KG	5,178.00	414 (E)	24/03/2005
19	DOXYCYCLINE HCL/ DOXYCYCLINE HYCLATE	KG	1,788.00	414 (E)	24/03/2005
20	DEXAMETHASONE (PURE)	GM	114.00	755 (E)	06/08/2001
20a	DEXAMETHASONE-11-21 PO4 (DI SODIUM)	GM	125.00	755 (E)	06/08/2001
20b	DEXAMETHASONE-TRIMETHYL ACETATE DTA	GM	158.67	481 (E)	02/08/1993
21	DICHLORO METAXYLENOL (DCMX)	KG	241.00	564 (E)	06/08/1997
21a	P-CHLORO METAXYLENOL (PCMX)	KG	284.00	414 (E)	24/03/2005
22	EPHEDRINE HCL	KG	1,314.00	768 (E)	07/07/2003
22a	EPHEDRINE RESINATE	KG	954.00	922 (E)	21/12/1994
22b	PSEUDO EPHEDRINE HCL	KG	1,967.00	768 (E)	07/07/2003
22c	PSEUDO EPHEDRINE SULPHATE	KG	2,535.00	435 (E)	16/06/1992
23	ERYTHROMYCIN (BASE)	KG	2,092.00	844 (E)	15/06/2005
23a	ERYTHROMYCIN THIOCYNATE	KG	3,072.00	84 (E)	11/02/1991
23b	ERYTHROMYCIN STERATE	KG	1,465.00	844 (E)	15/06/2005
23c	ERYTHROMYCIN ESTOLATE	KG	2,063.00	844 (E)	15/06/2005
23d	ERYTHROMYCIN ETHYL SUCCINATE	KG	2,892.00	844 (E)	15/06/2005
43	PHENIRAMINE MALEATE	KG	1,107.00	1,838 (E)	29/12/2005
44	PYRANTOL PAMOATE	KG	1,204.00	1,305 (E)	14/09/2005
45	PENTAZOCINE	KG	33,663.00	414 (E)	24/03/2005
46	PHENYL BUTAZONE	KG	352.00	1,133 (E)	15/10/2004
47	PENTOXYPHYLLINE	KG	2,013.00	591 (E)	23/05/2003
48	RIFAMPICIN	KG	3,560.00	1,840 (E)	29/12/2005
49	RANITIDINE HCL	KG	625.00	842 (E)	15/06/2005
50	STREPTOMYCIN SULPHATE BASE	KG	2,381.00	837 (E)	15/09/2000
51	SULPHADIMIDINE	KG	460.00	590 (E)	12/08/1994
52	SPIRONOLACTONE	KG	25,667.00	414 (E)	24/03/2005
53	SULPHADIAZINE	KG	565.00	564 (E)	06/08/1997
53a	SILVER SULPHADIAZINE	KG	3,596.00	846 (E)	18/11/1992
54	SALBUTAMOL SULPHATE	KG	4,819.00	1,303 (E)	14/09/2005
55	SULPHAMETHOXAZOLE	KG	323.00	1,299 (E)	14/09/2005
56	SULPHAMOXOLE	KG	589.00	414 (E)	24/03/2005
57	TRIMETHOPRIM	KG	840.00	1,839 (E)	29/12/2005
58	TOLNAFTATE	KG	4,167.00	412 (E)	24/03/2005
59	VERAPAMIL HCL	KG	4,109.00	564 (E)	06/08/1997
60	VIT. A PAMITATE (OILY LIQUID) [1.0/1.7 MIU/GM]	1,000 MIU	2,427.00	414 (E)	24/03/2005
60a	VIT. A ACETATE - (OIL LIQUID) [1.0 MIU/GM]	1,000 MIU	2,535.00	414 (E)	24/03/2005
60b	VIT. A ACETATE (DRY POWDER) [0.5 MIU/GM]	1,000 MIU	3,393.00	414 (E)	24/03/2005
61	VIT. C PLAIN	KG	396.00	1,304 (E)	14/09/2005
61a	VIT. C COATED	KG	382.00	1,304 (E)	14/09/2005
61b	SODIUM ASCORBATE	KG	412.00	1,304 (E)	14/09/2005
62	VITAMIN E ACETATE	KG	905.00	414 (E)	24/03/2005
63	VITAMIN B2 (RIBOFLAVIN)	KG	972.00	1,300 (E)	14/09/2005
63a	VITAMIN B2-5 PHOSPHATE	KG	2,217.00	1,300 (E)	14/09/2005
64	VITAMIN B1 HCL	KG	1,418.00	1,102 (E)	23/12/1998
64a	VITAMIN B1 MONONITRATE	KG	1,160.00	1,102 (E)	23/12/1998

Appendix Four: Active Pharmaceutical Ingredient Price Volatility

In 2008-2009, API pricing has experienced higher than normal volatility.[103] Multipurpose API manufacturers can change product lines in a matter of days or weeks. Therefore, if the margin on one API gets too low, for whatever reason, an API manufacturer can shift away from making it. This volatility is due to:

- ***Volatility in the cost of raw materials.*** Firms use a variety of raw materials to create an API. Some raw materials are:
    - ***Crude Oil:*** For example, paracetamol is derived from coal tar or crude oil.
    - ***Agricultural products:*** For example, one API from Piramal Health Care in India is based on the price of yams in China.[104]
    - ***Commodities:*** For example, yellow phosphorous is used in some APIs. The price increased from $900 per ton in June 2005 to $9,000 per ton in June 2008.[105]

  As the price of these input costs varies, so does the API final price. The impact of the raw materials on price varies per API.
- ***Increasing regulatory standards:*** Regulatory agencies in both China and India are raising standards and, in some cases, forcing manufacturers who cannot meet these quality requirements to leave the market.[106]
- ***Country risk:*** Chinese firms manufacture many raw materials and this concentration in one country increases the country risk. For example, for the six months before the 2009 Olympics, the Chinese government restricted the amount of waste water firms could produce in order to have a cleaner environment for the Olympics. This forced raw material firms to cut back and some prices rose up to 300%. As prices changed so rapidly, many final formulators were forced to pay and lock in a price at the time of order, not at the time of delivery. As a result, companies stockpiled, there were shortages, and then as supply came back on-line, prices dropped, but not to the pre-Olympic level.[107]
- ***Increasing environmental protection:*** As countries like China become more concerned with environmental protection, the cost of manufacturing both the raw materials and the APIs increases. Also, increased environmental costs favor larger manufacturers who can allocate these costs across a larger volume.[108]

API price volatility is expected to decline as fluctuations from the Olympics fade, but volatility due to exchange rates, oil prices, etc. will still remain.[109]

Appendix Five: Specific Active Pharmaceutical Ingredient Markets

The API market is not one uniform market, but varies dramatically by product and quality level. Therefore, while some API markets function quite efficiently, others may be less straight-forward. This appendix details some sample API markets and is in no means exhaustive. Further study of each is required.

Neglected Disease Drugs

Praziquantel

Praziquantel (PZQ) is a drug for controlling schistosomiasis. In 2009, DFID investigated scaling up treatment of schistosomiasis, since health need for the drug far exceeded the available PZQ supply. DFID determined that donor financing, rather than an industry supply constraint, was the bottleneck to scale up of PZQ provision. They felt that additional PZQ supply – at least 100M extra tablets - could be made available quickly if financing were made available.[110]

In 2007, 163M tablets of PZQ were sold. The Schistosomiasis Control Initiative purchased 50% of this for distribution in Burkina Faso, Mali, Niger, Tanzania, Uganda, and Zambia, the Chinese market purchased 30%, and Egypt, Brazil and a collection of smaller countries purchased the remainder.[111]

The patent on PZQ has expired and competition has driven down the purchase price for the 600mg tablet to 8 cents by 2009. Shin Poong (Korea) is the only vertically integrated manufacturer, manufacturing both the API and the finished product in tablet form. The other formulators purchase their APIs from one of the API manufacturers: Shin Poong (Korea), HaSun, Nan Jing, Hallochem Pharma (China), Kingland Chemicals (China), Chuming Pharmaceutical (China), Nantong Chem-Tech (China), Hangzhou Minsheng (China) and Shanghai Pharma (China). Manufacturers on the formulation side include: Shin Poong (Korea), CIPLA (India), E. Merck (Germany), EIPICO (Egypt), BDH Industries Limited (India), Sinochem Jiangsu Corporation (China), and Purepharma (India). In addition, two Tanzanian companies have begun to develop PZQ using low cost raw materials from China and Korea. In 1993, Shin Poong was known to be the largest global producer of PZQ, however current market shares for the producers are unknown.[112]

Insecurity regarding the sustainability of donor financing for PZQ purchase has decreased this market's attractiveness from a producer's standpoint. DFID is concerned that E. Merck's generous commitment to donate 20M tablets per year may decrease countries' finance allocation to PZQ purchase, effectively decreasing market size. DFID would prefer sending a signal of predictable financing to maintain secure and competitive supply.[113]

Program Drugs (HIV/AIDS, TB, and Malaria)

The markets for program drugs are relatively centralized, well-managed and growing. Large financing agencies such as The Global Fund to Fight AIDS, TB, and Malaria (Global Fund); The President's Emergency Plan for AIDS Relief (PEPFAR) and UNITAID manage most of the capital to assist developing countries to buy program drugs. These international financing agencies require that governments which use their funds to procure drugs, purchase only drugs that have an international certification, either WHO PQ or approval from an SRA.
Currently, local Sub-Saharan manufacturers capture only a small share of the donor market (estimated to amount to a total between $750 million and $1 billion). As of April 2007, only two Sub-Saharan African manufacturers (South Africa's Aspen Pharmacare and Sandoz Pty) had WHO prequalified products, and these two Sub-Saharan African manufacturers produced only 11 of the 248 WHO prequalified HIV, TB, and malaria medicines. While several manufacturers in the region are seeking prequalification, it is a difficult process, and one that is relatively more expensive for a smaller manufacturer.[114] Furthermore, once a firm achieves these certifications, it is not guaranteed business but rather only becomes eligible to apply for a tender where the firm may be, for example, one of eight firms applying.[115]

The API market for these drugs is relatively robust. Most concerns revolve around quality standards more than the supply of the API. Possible situations where the supply of APIs for HIV/AIDS, TB, or malaria may be impacted include:

- ***Tender cycle issues:*** Many international tenders work on annual or biannual cycles. When a firm wins a tender, it is locked into a price and given a volume estimate. In some cases, the volume is guaranteed; in other cases it is just an estimate. This uncertainty is a challenge.
- ***Supply Chain timing risks:*** When a final formulator submits a tender, they will get a price estimate from their API supplier but may not be able to lock in that price. The formulator may have to wait from six months to a year between submitting a tender and winning it. However, API firms do not like to hold price quotations firm longer than 1-2 months due to currency fluctuations, changes in export subsidies and tight controls on foreign currency.[116] Final formulators will incorporate this risk in their pricing. There have been cases where final formulators have won tenders and then had difficulty in supplying at the tendered price due to increased API prices.[117]
- ***End-market predatory pricing:*** Due to the competitive nature of some drug markets, some final formulators may prices below where the market can sustain.[118]

A risk is that many developing country governments are pushing for local manufacturing of ARV drugs. This could open this space up to non-prequalified manufacturers. In general, if the quality of the final formulator is in question, the quality of the API manufacturer is even more questionable.

Anti-HIV drugs

Approximately 900,000 people are currently on ARV therapy worldwide, 500,000 of whom are in developed countries. While Indian firms supply the API or the finished product for less than half of the total, they supply a much larger percentage of the product to patients in developing countries. Additionally as developing countries continue to scale-up treatment, in the near-term, many of these APIs will come from India, while Chinese and South African suppliers are also on the horizon. This will make the marketplace more competitive generally, at least for the older ARVs.[119]

On the other hand, the market for newer ARVs is likely to become less competitive over time, since TRIPS (Agreement on Trade Related Aspects of Intellectual Property Rights) implementation in major producing countries like India will make generic copying of patented products illegal. The result is likely to be bifurcation of the market for ARVs, with single-source products on the one hand and competitively supplied products on the other.[120]

Many international organizations and NGOs are working within this space to ensure access to quality drugs. Examples include UNAIDS, PEPFAR, UNITAID, the Global Fund, and the Clinton Foundation.

> ***Case Study: Clinton Foundation and HIV/AIDS drugs:*** When the Clinton Foundation's HIV/AIDS team, the Clinton HIV/AIDS Initiative (CHAI), decided to tackle access to HIV/AIDS drugs, approximately 70,000 people were being treated in the developing world. Manufacturers could not get scale economies in production and charged high prices for the drugs. CHAI worked both with African and Caribbean governments to obtain intentions to purchase large orders if final formulation manufacturers offered lower prices, as well as with final formulators, offering them a much larger and less-volatile market for AIDS drugs in return for lower prices based on the projected higher volume. While brand-name pharmaceutical companies were not interested, some generic manufacturers in India and South Africa were. The Foundation worked with these firms to bring costs down and, in the words of President Clinton "was (able) to get them to go from what I call a 'jewelry-store model' to a 'grocery-store model'—from a high-profit, low-volume, uncertain-payment business to a low-margin, high-volume, certain-payment business."[121] Yusuf Hamied, chair of Cipla, said that his firm was attracted to the foundation's plan because it ensured high-volume, predictable contracts in developing countries, which were otherwise seen as non-commercial markets.[122]
>
> ***Case Study: The Global Fund launches a Voluntary Procurement Program:*** In 2007, the board of the Global Fund mandated the Global Fund to address drug procurement challenges with a new voluntary procurement program. This pooled procurement recognizes that individual countries, particularly smaller countries, buying Global Fund-financed drugs often have little leverage from a costing perspective.[123] When operationalized, this

program may have some interesting possibilities for products that are usually purchased in small volumes.

Anti-TB drugs

The Global Alliance for TB Drug Development reported in 2000 that the world spent $470M on first- and second-line TB drugs. An estimated 30% of that was in the public/tender market, and 13% came from international donor assistance.[124]

First-line TB drugs

The standard "short" course treatment for TB is isoniazid, rifampicin, pyrazinamide, and ethambutol for two months and then isoniazid and rifampicin alone for a further four months. The first-line TB drug cost is about $10 per patient for the entire course. No new first-line TB drugs have been brought to the market in the past 40 years and all the drugs are currently off-patent, therefore pricing should be close to production costs and the market competitive.

The Global Drug Facility (GDF), an initiative of WHO and the Stop TB Partnership, determined that the 2002 total first-line anti-TB drug market size was $341-$384M, and the public/tender market was approximately $66M.[125]

The GDF aims to increase purchasing leverage through creating and pooling demand, helping to standardize treatment regimens, and providing some financing. And since the market is already competitive, the one-third price reductions that GDF has achieved (on average) are less than what can be achieved by programs focused on increasing access to drugs supplied by a single source.[126]

Second-line TB drugs

Second-line TB drugs include aminoglycoside; antibiotics such as amikacin or kanamycin; polypeptide antibiotics such as capreomycin, pyrazinamide, ethambutol; fluoroquinolones such as moxifloxacin, rifabutin, cycloserine; thioamides such as prothionamide or ethionamide; PAS; macrolides such as clarithromycin, linezolid; high-dose INH; interferon-γ; thioridazine; and meropenem and clavulanic acid.[127] Challenges with second-line TB drugs include the fact that most of these drugs have only one supplier for each (as they can be technically challenging to reverse engineer and/or are on patent). This makes competitive tendering challenging and results in increased purchasing leverage and/or securing differential pricing agreements as one of the few options to increase price / access.[128]

WHO's Green Light Committee (GLC) pools demand, structures partnerships and negotiates on behalf of countries in a situation where demand is small and extremely fragmented. Recognizing the differing market structures for MDR TB drugs, GLC tailors its supplier approach to the market situation. For drugs that can be competitively sourced, a GDF type bulk purchasing approach is used. For drugs

that are single-sourced or patented, a negotiation approach is used, based on quality and price criteria, while longer-term, more competitive supply options are sought. To maintain a competitive marketplace and ensure sustainable supply, GLC, utilizing GDF as a procurement agent, awards a large percentage of its tender to the quality-assured company with the lowest-priced drug, and a proportional percentage to one or a few of the remaining quality manufacturers. GLC also looks for opportunities to induce new suppliers to enter the market, thereby increasing competition. This was done successfully with manufacturers of capreomycin and cycloserine, both formerly exclusively produced by Eli Lilly, as well as with a third drug known as PAS. GLC's strategy has increased supply and decreased the price of quality-assured MDR TB drugs. GLC has managed to achieve 85 - 99% reductions on US prices of the 14 products procured for GLC-endorsed projects. Drugs for an entire 2-year course of therapy now cost US$ 500 - 1500.[129]

Antimalarials

Several families of drugs are used to treat malaria. Chloroquine was the anti-malarial drug of choice as it is very cheap and effective. However, increasing chloroquine resistance has made chloroquine, quinine and amodiaquine less effective. Extracts of the plant Artemisia Annua (A. Annua), containing the compound artemisinin or semi-synthetic derivatives offer over 90% efficacy rates. Since 2001, WHO has recommended using Artemisinin-based Combination Therapy (ACT) as first-line treatment for uncomplicated malaria in areas experiencing resistance to older medications. While numerous countries, including most African nations, have adopted the change in their official malaria treatment policies, cost remains a major barrier to ACT implementation as ACTs cost up to twenty times as much as older medications. It has been estimated that 80% of ACT cost is tied up in the API.[130]

The high cost is partially due to ACT supply not meeting demand. Demand is high - one estimate suggests 300-500M cases of malaria in Sub-Saharan Africa and, assuming 60% of these cases are appropriate for ACT, this means a total demand of treatment for 180-300M cases. Supply is lagging since enough raw material was available in 2006 to generate only 20-30 million treatment doses. A primary driver of this shortage is demand uncertainty: there is an 18 month lag between planting seeds and getting final products to the market. Usually, in demand uncertainty situations, producers adhere to the most conservative demand, and manufacturers who might otherwise enter production of ACTs do not. In 2007, there were few manufacturers: 6 producers of raw materials (3 in Vietnam, 2 in India, 1 in China) and 12 producers of ACT finished product of differing combinations (4 in Europe, 7 in Asia, 1 in Africa).[131]

The following international initiatives are currently in place to address these market challenges:[132]

- ***Affordable Medicines Facility – malaria (AMFm)****:* The AMFm is a brand new innovative financing mechanism, housed in the Global Fund, which aims

to expand access to ACTs by providing a prepayment to ACT manufacturers that will act as a credit when private, public and not-for-profit buyers make their purchases for eligible countries. In 2008, MSF issued a statement warning that unless AMFm preparedness planning includes API manufacturers, the AMFm could increase demand of ACT to the point of creating a global artesimin shortage.[133] A Roll Back Malaria technical paper, adopted the same day as the MSF warning, noted that given the planting cycle of the A. Annua, decisions on the surface areas that need to be planted will need to be made before the end of 2008 in order for planting to begin in early 2009, and also noted the potential for a global shortage.[134] UNITAID is leading development of a more detailed forecast of ACT demand and supply for Phase 1 roll-out of the AMFm, which began in April 2009.

- ***WHO / Novartis Partnership:*** WHO and Novartis have partnered to provide Coartem (artemether-lumefantrine, a patented combination) at 'cost' pricing of $2.40 per adult for 10 years. WHO reduces risks and costs for Novartis by providing expert reviews, funding and technical assistance to make the product better suited for target market, monitoring leakage, assisting with collecting pharmacovigilance and post-marketing surveillance data, and by reducing the transaction costs. WHO also forecasts demand and provides a credit fund to help countries pay for Coartem.
- ***The Global Fund:*** The Global Fund committed $30M from 2001-2006 for African countries to purchase ACTs in the first three proposal rounds. In the fourth round of Global Fund applications, there was a sharp increase in approvals that included funding for ACT treatments, leading to approved funding for 122M treatments. This has shifted the primary problem from a financing shortage to a supply shortage.
- ***Malaria Medicines Supply Service (MMSS):*** The MMSS service has recently been formed in WHO to try and address the ACT challenges. MMSS will incorporate the following functions:
    - Financing: MMSS plans to work with countries to get firm support for virtual pooling of funds through pledges and other means; to explore other options to negotiate concessionary pricing or other favorable terms from suppliers using a bilateral negotiation/firm contracting approach; establish a resource mapping exercise and, if necessary, explore a time-limited purchase fund for ACT (preferably within existing structures), given the critical need for market stimulation and rapid expansion.
    - Supply chain management: demand forecasting, support for fast-tracking in-country registration, pre-qualification of manufacturers / products, a database on sources and prices; and technical support on procurement planning.
    - Technical tools.
    - Provision of global information products.

Non Program Drugs

Paracetamol

Paracetamol, derived from coal tar, is one of the most important non steroid anti-inflammatory drugs. Chinese paracetamol exports, valued at $44.8M, have increased 13% year-on-year to 12,557 tons during the first quarter of 2009. The average export price stood at US$3.6 per kilogram during this quarter, with a year-on-year growth of 5%.[135] Africa imported $6M of this, which is a 15.7% increase from the year before. Exports to Nigeria alone increased 41.3% to US$3.4 million.[136]

While China has more than 100 paracetamol exporters, they are hampered by out-of-date manufacturing processes. Excessive production capacity and low product quality make it difficult for Chinese paracetamol producers to expand into high-end markets outside of China. Without access to new markets, China's domestic paracetamol manufacturers have been forced to grab market share through a price war[137]

Although 30-40% of the world's total paracetamol final formulations are made in China, many African firms make it as well. African final formulators can also find many paracetamol API sources.

Endnotes

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