PDP MANUFACTURING AND SUPPLY STRATEGIES

A DISCUSSION PAPER

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Abstract

The Access Steering Committee of the Product Development Partnerships (PDPs) commissioned this paper on "PDP Manufacturing and Supply Strategies." This paper discusses the approaches that PDPs currently use to ensure the secure manufacturing and supply (M&S) of quality products at an affordable price, once their products have received regulatory approval.

Eleven PDPs were interviewed in preparing this paper, working on a range of vaccine, medicine, microbicide and diagnostic products. Three key stakeholders were also interviewed. M&S strategies and approaches vary widely among the PDPs interviewed, mostly by

- stage of product development
- organizational experience with previous product approvals and launches
- marketplace readiness for innovative products
- technologies used for manufacturing

Establishing low-cost, high-quality, sustainable supply is the goal of all concerned. PDPs, focusing on product development programs, can be challenged with evaluating and selecting manufacturing and supply partners for access activities, and must also anticipate manufacturing planning early in their development processes, often before a competent manufacturing partner has been found.

PDPs have established a wide range of manufacturing and supply models that have been driven by the characteristics of the PDP's product and the markets they serve. The majority of PDPs do not anticipate playing an active role in the manufacture and supply of their products once they have been approved, as they expect their partners to manage manufacturing and supply responsibilities, together with fulfilling the role of the market authorization holder. Nevertheless PDPs and their manufacturing and supply partners should be fully aligned. Although many PDPs do not want to be deeply involved in planning manufacturing capacity and supply issues, evidence shows that a good understanding of these challenges and the technology involved can be instrumental in ensuring the secure supply of low-cost high-quality products. Some PDPs also play a key role in identifying distribution partners and facilitating entry of their manufacturing partners into public markets.

Licensing and contractual agreements with manufacturing partners offer a mechanism to shape the division of labor between PDPs and partners and ensure the continued supply of low-cost high quality product. These agreements should be proactively evaluated and carefully negotiated. By addressing contentious issues and potential plans for engaging additional manufacturers early, PDPs can develop more stable partnerships.

Matching the not-for-profit development and the for-profit commercial worlds can be easier where commercial partners have the economic depth and the corporate will to support low-cost and low-margin manufacture for the long term. In situations where manufacturing and supply partners may not have the same financial ability and corporate willingness, PDPs have helped negotiate financial incentives to support the establishment of supply chains. This latter case, however, highlights a key finding from the research for this paper: the need for PDPs to plan for the long-term sustainability and security of product supply, beyond the initial launch period.

Manufacturing capacity requirements for new products must be defined early, taking into account the long lead-times typically required to establish new manufacturing facilities and equipment. To accomplish this, the business case for the

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introduction of the innovation must be based on solid analysis and projections. The relationships between product price, market demand and health resources must be fully understood.

The integration of achievable target prices into Go/No Go decisions of the original development process can be challenging for product developers. Building robust demand scenarios early on, although often difficult, supports the business case for development of manufacturing capacity and product introduction, and such scenarios provide strong leverage in negotiating the commitment of manufacturers to price targets.

PDPs should further cultivate ways to confidentially share information among themselves about the manufacturing and supply agreements established with their partners. They also should consider the long-term stewardship of the products, once the PDP itself will no longer be responsible.

INTRODUCTION

Product Development Partnerships (PDPs) and their donors recognize that ensuring access to new products is a complex and challenging task. Because of the importance of establishing secure low-cost, high-quality manufacturing supply chains and of ensuring their products can be distributed to the people who will most benefit from them, the PDP Access Steering Committee commissioned this paper (See Annex 5 for Terms of Reference). The purpose of this Manufacturing and Supply (M&S) discussion paper is to explore and document PDPs' experiences and challenges, with regard to the manufacturing strategies and approaches taken to ensure access and availability of new products. Specifically, this paper discusses the range of strategies employed by the various PDPs, and their rationale.

The authors of this paper bring their broad experience in PDPs and the pharmaceutical and biotech industries where they have developed and implemented manufacturing and supply strategies for pharmaceutical products. They interviewed eleven PDPs:

- Four are developing vaccines.
- Five are developing medicines.
- One is developing preventative microbicides.
- One develops diagnostic products.

The PDPs were asked a series of questions about the manufacturing and supply strategies they employ for their late-stage development and launched products. (Refer to Appendix 4i for these questions.) The authors also interviewed three key stakeholders: the Bill and Melinda Gates Foundation, the Clinton Health Access Initiative and the World Health Organization. (Refer to Appendix 4ii for these questions.) All PDPs and stakeholders interviewed for this paper are listed in Appendix 2.

This paper explores the following subject areas, as they form the basis of robust manufacturing and supply strategy:

1. Organizational Roles and Responsibilities
2. Manufacturing and Supply Contracts
3. Product Launch Plans
4. Understanding Demand
5. Understanding Manufacturing Capacity
6. Additional Manufacturing and Supply Partners
7. Cost Of Goods
8. Technical Stewardship for Approved Products
9. Supply Chain Management
10. Distribution

For each subject area, the authors discuss their findings from the interviews and make recommendations on how PDPs together with their partners should address the subject and cite specific examples of PDPs' approaches to the subject.

(The terms of reference for this paper are included in Appendix 5. The development and lifecycle phases of the products being developed by the PDPs interviewed are listed in Appendix 3. Where relevant, documents both formally published in literature and those of various agencies are referenced in Appendix 6.)

1. ORGANIZATIONAL ROLES AND RESPONSIBILITIES

Interview Findings

PDPs follow one of two different organizational designs for the manufacturing and supply strategies for their products:

- Most often, the commercial partners have the responsibility for manufacture, registration, supply and distribution of the product.
- Sometimes PDPs and their partners share responsibility for development and manufacture, with registration and distribution responsibilities being split between the PDP and their partners, depending on the countries in which the product will be made available.

With very few exemptions, PDPs do not take on the role of Market Authorization Holder (MAH). This role usually falls to their commercial partners, who are often also the product manufacturers.

The involvement of the manufacturing partner over the life cycle of product development varies considerably. As detailed in Figure 1, some manufacturing partners supply the product all the way from the clinical trials through to launch and broader distribution, while others have a limited involvement prior to market authorization.

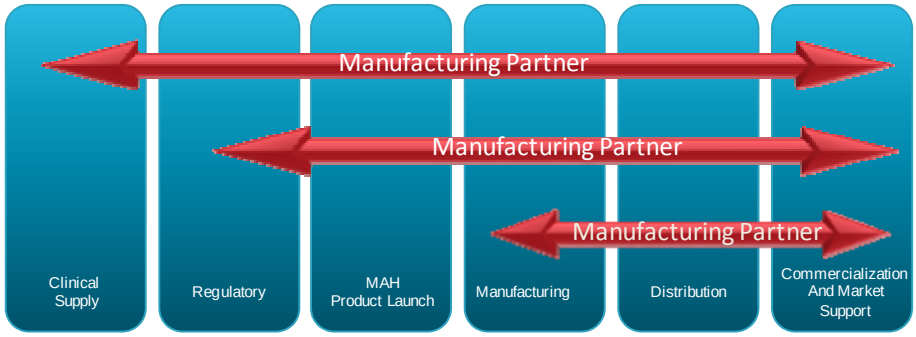

Figure1. Engagement models of PDPs Manufacturing Partners from clinical supply to Product Use

Some PDPs seek to develop comprehensive manufacturing and supply plans that identify the manufacturing and supply responsibilities for the product early in its development lifecycle. In some cases, manufacturing and supply responsibilities are defined in formal written agreements between the various product development, manufacturing and supply partners; in other cases, the manufacturing and supply strategy is not formalized, remaining the responsibility of the manufacturer, with no significant interaction with the specific PDP. This lack of formal agreement can lead to ambiguity and potential disruption of supply, if roles and responsibilities are not clearly defined and agreed to by all parties.

Responsibility for management of the manufacturing and supply relationships with partners tends to be established within each PDP. Some PDPs establish joint governing committees together with their manufacturing partners to cooperatively manage the collaboration. PDPs report that it improves the planning process for all parties to define the strategy and responsibilities following proof of concept, which typically occurs during phase II clinical studies, and thereafter remaining in an ongoing dialogue with partners as the relationship evolves.

Developing and operationalizing the PDP's role in support of manufacturing and supply is a complex process. Some PDPs have built dedicated specialized teams for such tasks as analyzing market intelligence, engaging manufacturing partners and supporting market launches. Some see their primary responsibility as one of catalyst, to ensure that planning for the future manufacturing and supply is put in place, that the downstream activities are funded and that there are concepts and plans beyond the early adoption (such as for optimizing supply and lowering cost of goods). A number of PDPs and stakeholders have discussed questions of how to best ensure long-term sustainable manufacturing and supply relationships that are not based on mere profitability.

Some PDPs feel that they have little leverage over their "Big Pharmaceutical" manufacturing and supply partners, relying instead on the altruistic nature and Corporate Social Responsibility (CSR) of companies to support the industrialization and supply of their products once approved. Suggestions for improving their leverage included:

- Engaging stakeholders like the Bill and Melinda Gates Foundation (BMGF) and the Clinton Health Access Initiative (CHAI) to reinforce the altruistic and reputational side of the relationship and specifically help identify the business potential that often can be realized through co-operation with the PDP.
- Ensuring that the team in the PDP responsible for managing the relationship is credible, preferably with many years of experience managing commercial operations and relationships.

PDPs would benefit from fully understanding the economic and non-economic factors driving their partner's decisions. The cost of establishing a product supply chain can be burdensome, and where their partners are driven by economic motives, PDPs have successfully used external funding to help establish the supply chain. In this way they keep it operational until demand grows to a point where the supply chain is self sustaining. This funding can be secured by various means, such as volume guarantees, take-or-pay contracts or funding specialist equipment and capacity expansions.

The obligation to ensure continuity of supply for potentially unprofitable low-volume products to address unmet health needs may create liability issues for the manufacturer. In addition to the cost of production, companies may face significant additional costs associated with GMP compliance, maintaining Chemistry Manufacturing and Controls (CMCs) regulatory documentation, and regulatory agency requests. Whilst larger pharmaceutical companies might be willing to fund these costs, for smaller companies this can create a considerable burden. Generally, PDPs with market experience realize that they must make the manufacturing and supply processes for innovative products independent of their own continued existence. As the vast majority of PDP funding is for product development, rather than for managing supply, a need exists to transition overall responsibility for lifecycle management in a way that is sustainable for their partners or others.

Transitioning the ongoing responsibility for products can be easier if the pharmaceutical partner has a large organization or a market interest in the relevant countries, as is true for some large pharmaceutical partners. However, transition can become challenging in cases where manufacturing partners have only a limited capacity to manage the product or where they are unwilling to take on these responsibilities for other reasons.

The Concept Foundation's experience in terminating the licensing agreement of a low-cost manufacturing partner, who was unable to maintain quality standards, highlights this risk. The transfer of technical and quality oversight to commercial partners is impossible, when they do not have the ability or willingness to maintain this responsibility over the long term. Thus, before transitioning the technical stewardship, PDPs should undertake a risk assessment of their partner's ability to support the product. If partners are unable to assume this responsibility, the PDP must identify a suitable party for technical stewardship during a product's lifecycle. However, often the issue remains unclear as to whom these successor parties might be.

Recommendations

Selecting appropriate partners as manufacturers, suppliers, distributors and market authorization holders (MAH) and clearly defining their roles and responsibilities is vital for successful launch and continuity of supply. These selections are best made, if possible, in the early stages of the development process. Most innovative pharmaceutical companies begin to develop their manufacturing strategy following proof of concept and once they have decided to fully develop the product.

The focus for the manufacturing and supply strategy is strongly dependent on the specific product. In the case of a new indication for an established product already being manufactured, the key strategic questions are

- How will the originator support the product once the new indication is approved?
- How are generic manufactures positioned to supply the product after patent expiration?

For a new product being manufactured for phase III clinical study materials, that manufacturer will usually be the initial supplier when the product is approved. In such cases, the strategic questions are then focused on ensuring

- sufficient capacity to support launch and rollout plans

- additional capacity as demand grows

Roles and responsibilities defined by the strategy should include the long-term technical responsibility for the product once it has been approved and launched. Thus a mechanism can be established by which PDPs can disengage from the technical stewardship for the product, whilst also feeling assured that the vital manufacturing and supply knowledge will be retained by their manufacturing partners. This subject is discussed in more detail in section 8.

Examples:

MMV

MMV does not have a template for formalizing their manufacturing strategy. However, they assess candidates for their product development pipeline with extensive due diligence reviews of a potential partner's ability to manufacture the product upon approval. Many of MMV's pharmaceutical manufacturing partners have already established strategies for MMV's products as part of their normal course of business. For example, Novartis made public a commitment before 2006 to supply up to 100 million of Coartem treatments per year. Novartis has invested in both its API sourcing and its manufacturing capacity to back up this commitment, and they are confident that they have sufficient capacity to manufacture the anticipated demand for the dispersal formulation of Coartem as well.

AERAS

Aeras have defined the manufacturing and supply responsibilities in formal agreements with their various development partners. Where Aeras partners are undertaking the drug product development work for a vaccine, the partners will be responsible for manufacture and supply following approval. Where Aeras is wholly responsible for the pharmaceutical development, they anticipate implementing a mixed model of manufacturing and supply responsibilities, with Aeras supplying some markets and Aeras partners that have vaccine fill finish capabilities responsible for supply into other markets/regions.

DNDI

DNDi cited the example of Artesunate/Amodiaquine fixed dose tablets (ASAQ) where Sanofi Aventis has responsibility for industrial development, registration, distribution and supply at cost to the public sector. Today, ASAQ is registered in 29 countries and 80 million treatments have been distributed. Sanofi Aventis, DNDi and MMV are now conducting an extensive field program in Ivory Coast to collect safety data, monitor efficacy and potential development of resistance. In addition, a technology transfer is in preparation to a sub Saharan manufacturer. See: http://dndi.org/press-releases/archives/777-dndi-sanofi-aventis-agreement.html and http://www.actwithasaq.org/en/press.htm

2. MANUFACTURING AND SUPPLY CONTRACTS

Interview findings

Generally, PDPs have licensing agreements rather than contract manufacturing and supply agreements with their partners. However, a limited number of PDPs plan on retaining manufacturing and supply obligations for some markets, in which case they will either manufacture the product themselves or establish contract manufacturing agreements with other partners.

In some agreements, PDPs retain the right to be involved in launch planning and in determining the priorities by which various countries are given access to a new product, although the responsibilities for executing the launch plans reside with their partners.

Some contractual obligations with manufacturing partners are centered on price commitments. These commit the manufacturers to supply product at cost and ensure that they will not make any profit on the sale of product to the public sector. Other contractual agreements allow for differential costs, or cost-plus pricing. Typically these agreements are established during the clinical development phase. Where pricing commitments have been made, contracts often contain a cost audit provision that allows the PDP to verify pricing. Several contracts also contain obligations to provide actual sales figures. This is particularly important if the PDP is actively involved in shaping the market and in aggregating forecasted demand for all markets. (For a detailed discussion on pricing, please review the following paper: http://www.conceptfoundation.org/files/Pricing Discussion Paper.pdf.)

Some agreements include specific terms that allow technical transfer of manufacturing processes to other parties, in the event that the partner is unable to meet demand or price requirements for product in specific markets. However, from the authors' experience, a potential problem exists with this type of clause in that, by the time a partner realizes they may have a supply problem it might be too late to avoid an impact on supply. Supply shortages and stock outs occur when transferring production to a third party and gaining the regulatory approvals required for supply from the alternative manufacturer. Hence adequate agreement is necessary to ensure that any risks to supply are mitigated early, through proactive oversight and management by the parties concerned.

A number of PDPs confirmed that their agreements gave them the rights to conduct annual Good Manufacturing Process (GMP) compliance inspections. They find these particularly important with some low-cost regional and local manufacturers who might not otherwise strive to maintain the appropriate quality compliance, without the knowledge that some external body might inspect their facilities.

In setting manufacturing and supply contract commitments, some PDPs report that their leverage with large multinational companies can be limited, but with smaller biotech companies, they find they have a greater leverage. This better leverage may occur because smaller companies tend to have limited funds, so they are keen to enhance the perceived value of their products and operations. They collaborate with PDPs, to show the potential market for their products and to demonstrate a broad spectrum of support. Some have used this leverage to gain market-access commitments from the smaller companies. These commitments include the rights to identify the countries in which their products will first be licensed.

On a general note:

Pharmaceutical companies have specific motivations for their cooperation with PDPs; maybe there is a champion, a specific technology or a history of engagement in specific disease areas. The effort of launching a not-for-profit drug in many developing countries might, however, not be their focus or in their long-term interest, so PDPs should think about sustainability early on. Thinking about licensing schemes with the partners is a critical step toward creating stable supply networks. Establishing these licensing schemes should not be mistaken for contingency planning. Rather, they are about understanding and shaping the market place. PDPs must understand the real motivations of the partners to see where other players can further support access to markets, when or where the partner does not really want to be actively engaged.

The majority of senior R&D staff in PDPs comes from innovator companies in the West, so their primary business relations tend to be with western companies. However, a number of PDPs have entered into business relationships with highly sophisticated low-cost manufacturers in emerging countries such as India and elsewhere. A number of stakeholders stress that this should be considered by all as it offers the opportunity to establish low cost sources at launch rather than later, as part of the subsequent roll out through technical transfer post approval.

Recommendations

Contractual agreements with manufacturing partners offer a wide range of mechanisms for shaping the manufacturing and supply architecture, for establishing pricing structures and for establishing alternative licensing agreements. These agreements should be thoroughly evaluated and carefully negotiated. These agreements should also retain the right to conduct financial audits to ensure pricing commitments are maintained. Concerns that cost-plus pricing agreements can limit the motivation of partners to reduce COGs can be alleviated by incorporating mechanisms that allow manufacturers to profit from increased saving. Agreements should also retain the right of PDPs to conduct independent GMP compliance audits, especially for regional or local companies that might otherwise let their compliance standards slip.

The issue of maintaining the commitment of the partners in no/low profit settings remains a long term challenge. Creating partnerships independent of internal champions and special relationships is demanding but crucial.

Examples

DNDI

Following an experience where a manufacturing partner terminated support for a product, DNDi's contractual agreements now stipulate that, if a pharmaceutical partner wants to cease manufacture and supply of the product, that partner must first find a suitable alternative manufacturer and must transfer production to the new manufacturer at the partner's cost.

MVP

The Serum Institute is contractually committed to meet the demand for MenAfriVac from UNICEF tenders. The anticipated UNICEF demand is based on the demand forecast provided by MVP. If the Serum Institute is unable to meet these volume commitments, they face penalties, and MVP has the right to transfer production to other manufacturers.

TB ALLIANCE

Moxifloxacin is an established Bayer Schering Pharma (Bayer) antibiotic that is marketed in 104 countries. The TB Alliance is collaborating with Bayer to add a TB indication to the label of moxifloxacin. By the time the new TB indication is approved, moxifloxacin will be off patent, and it is expected that generic manufacturers of moxifloxacin will have established a supply base. The TB Alliance is therefore considering whether they should establish additional partnerships with the generic manufacturers to make TB-specific combination therapy blister packs.

3. PRODUCT LAUNCH PLANS

Interview findings

Responsibilities for launching new products differ by PDP and by product. The extent to which PDPs play an active role in the launch of their products in individual markets is highly dependent on the expertise available from their partners. In some cases the PDP has no role in launching, while in other cases there is a deep involvement in both planning and executing the launch.

Often the manufacturing partner will also be the MAH and will launch the product. Some PDPs help their manufacturing and supply partners better understand specific market launch requirements and also help in resolving issues that might delay or constrain product roll-out and launch. For example, they might

- resolve manufacturing capacity constraints by helping partners develop business cases for capital investments
- help government agencies establish in-country logistics
- help manufacturing partners to register products, select distribution and other partners
- provide manufacturing partners with demand forecasting figures for specific markets

Key stakeholders suggested that launch planning should include supply planning well beyond launch. PDPs should also include practical plans to clearly delineate a path to broader availability and uptake of products, rather than focus only on the initial markets and easy-to-serve populations.

Recommendations:

Launch strategies reflect whether products are substituting for previously available and established products with the same indication or are new products intended for new indications. Accordingly, the need varies significantly for PDPs to support product distribution and guide its use and uptake.

Launch plans should include:

- Supply security and robust access provisions
- Phased registration and product rollout with widespread registration, including in low-volume countries
- Involvement of third parties and KOLs in product positioning and marketing/social marketing
- Shift in focus toward the end user
- Engagement with governments, offering analytical support in how to roll out and use these products
- Help to establish in-country distribution networks where appropriate
- Actions to further decrease costs over time
- Incentive structures to engage manufacturing and supply companies
- Contaminated waste removal where appropriate

PDPs and their partners should develop robust and comprehensive rollout plans that clearly identify milestones and responsibilities for supplying various countries and market segments. Launch plans must be closely linked to manufacturing and supply capacity plans; otherwise, the launch might be constrained by lack of product. Establishing clearly defined country and regional roll-out plans give the manufacturing and supply partners the ability to establish their capability in anticipation of launch. PDPs must appreciate that the lead time required to establish capacity can be measured in years in industry, so outline launch plans should be established to provide guidance to manufacturing partners during phase II of development. As the product progresses through phase III towards registration, launch plans are refined to provide the PDPs' partners with the information they need to establish their supply chains.

Where manufacturing partners lack the experience of launching new products outside of their immediate markets, they may require more active support, to help them understand registration requirements and to establish commercial relationships with other local or regional companies for marketing and distributing products in the other markets.

Examples

MVP

MenAfriVac was launched in Burkina Faso on the 6th December 2010, and it will ultimately be launched in 25 countries. The roll-out is expected to take about six years, as individual countries gain regulatory approval and the infrastructure is established for distribution and supply of the vaccine in the various countries where Meningitis is endemic.

In the recent launch in Burkina Faso, 5 million people were vaccinated within the first 4 days following launch. This represented 40-45% of the target population. This accomplishment was a significant manufacturing and logistical challenge. MVP worked with their partners to establish in-country cold-chain distribution capability; they helped establish waste stream destruction capability; and they helped drive public awareness to generate demand for their vaccine.

MMV

MMV recognizes that some of their smaller partners may not have the institutional capacity to engage in multiple parallel product tenders in several countries at the same time, and subsequently to assure pharmacovigilance support for product use in malaria endemic countries. In working with these partners to devise appropriate and impactful launch plans, MMV encourages and facilitates their outreach to cultivate partnerships with larger companies to address these gaps.

4. UNDERSTANDING DEMAND

Interview Findings:

As guidance for establishing robust manufacturing strategies, all the stakeholders interviewed stressed the need for PDPs to develop a thorough understanding of demand for their products, as well as the willingness of payers, governments and others to purchase and use a product once it is approved. The PDPs interviewed had a broad spectrum of understanding of the potential dynamics of demand. Some have very comprehensive demand models based on epidemiological data, conversations with potential payers, governments and NGOs, whereas others have simplistic demand projections with limited supporting research or evidence.

Without well-developed demand forecasts, it is impossible for manufacturers to decide on the size of the manufacturing capacity that they need for their manufacturing processes. MMV described Novartis's experience on first launching an ACT into the public market. Responding to loosely constructed demand forecasts from launch partners, Novartis scaled up their manufacturing capacity from 4 million to 50 million treatments in less than two years. Unfortunately, when orders actually materialized, demand was less than 10 million treatments during this timeframe, and Novartis was left with significant quantities of excess API and manufactured product on hand.

Numerous similar examples occur in industry, where manufacturing was planned on limited data, which resulted in manufacturing costs being significantly higher than anticipated. In these cases, batch sizes and the manufacturing process could not be optimized. Sometimes launch plans were constrained because of a lack of manufacturing capacity, or significant stock write-offs occurred because of over production.

A number of PDPs noted that the development of country-specific demand forecasts remains a challenge in many markets because of a lack of information on the levers of demand. These levers include potential market size, uptake projections, donor and local government commitment to purchase the new product, user preferences, competing products, and health policy changes. A number of initiatives have been established to improve this flow of information, as described below.

Recommendation

All PDPs should develop demand projections very early in the development process, ideally before product development starts. The lack of robust data upon which to build the demand forecast should not discourage the effort to begin demand forecasting, because the model can be optimized as more robust data becomes available. However, to avoid a Novartis Coartem scenario (see above), PDPs should always be clear with manufacturers about the reliability of the demand forecast and make clear which figures are less reliable.

To steer the manufacturing strategy accordingly, PDPs should use their product expertise to assess the overall market need, using such information as epidemiological data, demographic profiles, etc. Then, from discussions with ministries of health, NGOs and other key stakeholders, they can develop a view of anticipated global demand for their products. As a product progresses through development, PDPs can improve the accuracy of their demand forecasts through detailed discussions with key stakeholders, by assessing the willingness of payers to purchase their products, and by modeling the impact of varying COGs and anticipated efficacy.

Prior to beginning phase III clinical trials, a clear understanding of expected demand for the product is necessary. This information is vital for discussions with funders and manufacturing partners, who need demand analysis to justify the cost of clinical trials and the capital investments needed to establish manufacturing capability. They also need to model the projected COGs at launch and at various other stages of the product lifecycle.

To understand the potential range and volatility of demand, a minimum of three strategic forecasts should be established to cover

- a baseline demand forecast based on an assessment of the most likely efficacy, product uptake, and launch and roll out plans
- an upside demand forecast based on greater efficacy, higher levels of early adoption, and increased willingness of funders and governments to pay
- a downside demand forecast based on lower efficacy, lower willingness to pay, slower rollout and flatter take-up

These strategic forecasts should be expressed in terms of yearly demand and projected five to ten years after launch. Where possible, they should be segmented by individual countries or in regional groupings, as well as by public and private markets.

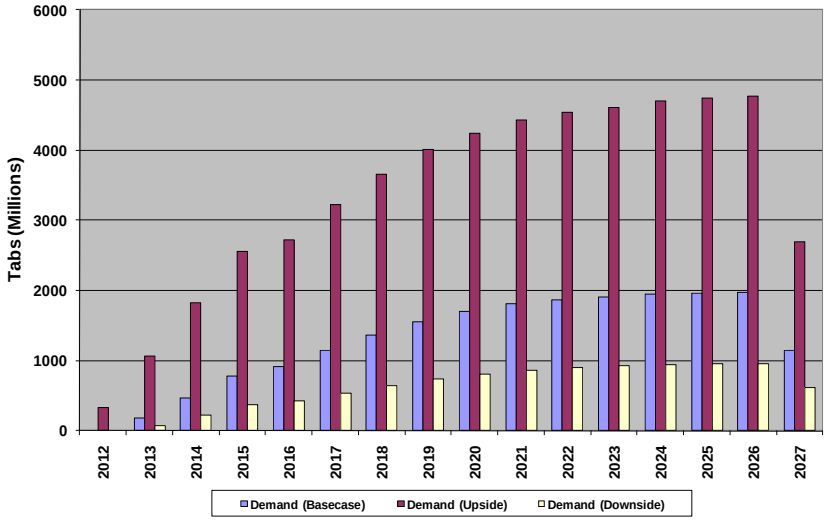

Figure 2 – Example of strategic yearly demand forecast

As illustrated in Figure 2, these three forecasts provide a "cone of potential demand." This information can be used by PDPs and their manufacturing partners to

- assess their capacity plans
- support business cases for the establishment of additional supply capability
- estimate the cost of goods

Examples:

PDVI

PDVI has developed a comprehensive model for estimating the potential demand for a dengue vaccine in endemic and non-endemic countries. The model was developed with epidemiological data on disease prevalence and a demographic profile within dengue endemic countries. The forecasts are segmented by public-sector demand, private-sector demand in endemic countries and private-sector travelers from non-endemic countries. Public-sector demand is further segmented into low, low-middle, and upper-middle income countries that are potentially eligible for funding under the Global Alliance for Vaccines and Immunization (GAVI) vaccine program. It also includes low-middle, upper-middle, and high income countries that are not eligible for funding under GAVI. The forecasts assume various levels of vaccine adoption and speed of rollout. They provide a range of potential demands for differing dosing scenarios and extend to five years from the availability of a licensed product.

PDVI recognized, however, that the adoption rates assumed within the model were much more aggressive than those that previous vaccine immunization programs had been able to achieve. So PDVI's forecast model needs further refinement as their dengue vaccines progress toward approval and launch.

MMV

MMV relies on global forecasting collaborations involving CHAI, MIT-Zaragoza and others to model global supply and demand forecasts based on country-level aggregation of anticipated demand and supply. Roll Back Malaria (RBM) and WHO have encouraged these market analytics to avoid supply chain problems globally.

MMV also recognizes that understanding the flow of products at the national level in malaria endemic countries is quite challenging, and very few governments in these countries are able to monitor the total volumes of treatments in their public and private sectors combined. MMV is working with two innovative pilot programs to monitor country-level importation of Artemisinin based combination therapies (ACTs) (partnering with IMS) and country-level distribution of ACTs in the public sector health system (with SMS for Life in Tanzania.) If they are successful, these efforts may yield solutions to the provision of quality data upon which to build future demand forecasts.

5. UNDERSTANDING MANUFACTURING CAPACITY

Interview Findings:

A number of PDPs have a clear understanding of how and when additional manufacturing capacity must be added and how this additional capacity can be funded. They are in ongoing discussions with their manufacturing partners. They understand the need to add manufacturers after launch, so that the security of product supply is established and that lower cost supply options are brought on line.

Other PDPs, for various reasons, rely wholly on their manufacturing partners to establish capacity plans. These PDPs do not play an active role in the plan development or review. Still others believe that phase III is too early in the development process to develop a meaningful capacity plan.

Recommendation

If the manufacturing partner is not an expert in the therapeutic area nor in the markets to be served, PDPs and their partners should jointly develop capacity plans, based on a sophisticated understanding of the demand dynamics. Their plans then can clearly show how manufacturing capacity has to be expanded to meet the demand forecasts. Often it is helpful for the PDP and partners to collaborate rather than work in isolation. In this way, the manufacturing partners can take decisions on adding capacity, and PDPs can confirm the timing of when other manufacturers should be added.

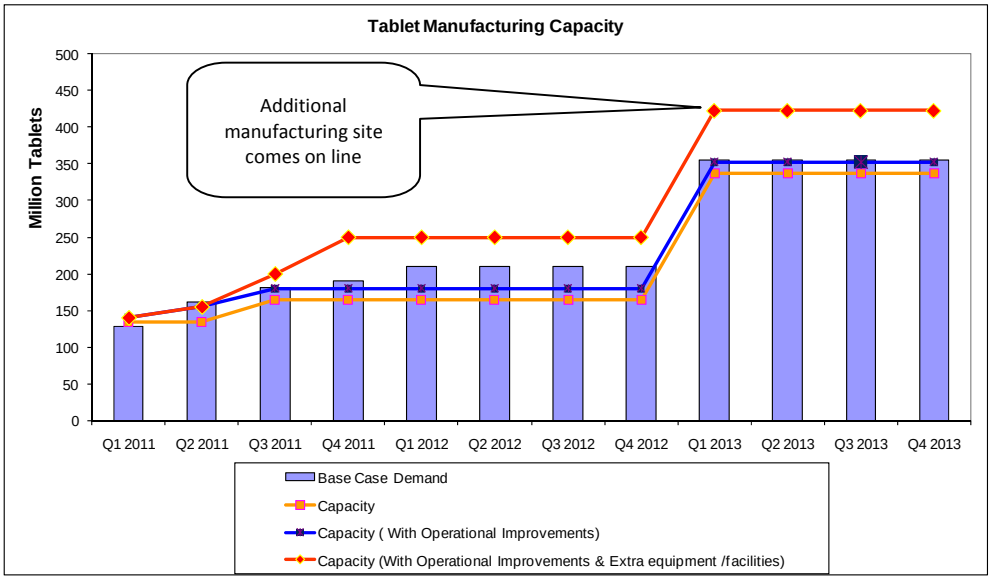

Figure 3 - Example of a capacity plan

Capacity plans are based on the best case demand scenario. These clearly identify when additional capacity must be operational to meet anticipated demand and when are the key milestone events that trigger the need for additional capacity. These plans should be constructed without excessive overcapacity, to limit unnecessary capital investments, which add unnecessary operating and depreciation to cost of goods.

Because of the long lead times required to establish new manufacturing capacity Pharmaceutical companies typically begin developing capacity plans for a product as soon as it passes the proof of concept milestone, which typically occurs during phase II clinical studies. Capacity plans should be revisited as demand forecasts are updated with new information. Capacity plans should also address how capacity can be expanded to meet the upside forecast, and equally, capacity plans should identify how capacity can be constrained for a downside forecast.

When entering into capacity discussions with manufacturing partners, PDPs must be frank about the possibility of adding manufacturers after launch, to establish a healthy, cost-competitive marketplace.

Examples:

PDVI

PDVI are working with Butantan, a Brazilian government-owned vaccine manufacturer, to help Butantan understand the potential demand for the US National Institutes of Health (NIH) dengue vaccine, to which Butantan have manufacturing rights. To meet demand for the vaccine, Butantan must establish sufficient capacity to supply a mass vaccination program for the at-risk population in Brazil. This capacity can subsequently be used to supply mass vaccination programs in other countries, as the likely roll out of the vaccine will be phased by registration and approval timelines in these other countries.

AERAS

Aeras and their manufacturing partners have developed capacity plans. Aeras have built sufficient capacity in their Rockville facility to meet worldwide demand for bulk recombinant BCG vaccine manufacture, and they intend to establish regional fill finish sites with partners.

6. ADDITIONAL MANUFACTURING AND SUPPLY PARTNERS

Interview Findings:

Several different reasons were mentioned for integrating additional partners into the manufacturing and supply strategy.

- Additional manufacturing capacity increases supply security, in case of unexpected production problems with the original manufacturers.
- Additional manufacturers can compensate where manufacturing partners do not meet their volume, quality or price commitments.
- Adding low-cost, high-quality manufacturers to lower the cost of goods and establish an independent supply base as an alternative to original partners.
- In larger markets, price decreases can potentially result from competition between several manufacturers as market forces come into play.
- If a product is not patent protected, generic manufacturers may want to produce and distribute the product.
- Local production may be a requirement or preference for purchase of the product.

Local manufacturing can be instrumental in motivating national healthcare systems to include products in their standard of care and formularies. In some countries it is even a prerequisite. Several PDPs noted an increasing interest in Africa in the last two or three years to establish local manufacturing. Local manufacturing is perceived as a potential way to resolve shortages, to make products available at affordable prices and to remove supply from the vagaries of multinationals and larger generic companies. However, the reality is that the prices of locally manufactured products can be considerably higher than those from global suppliers due lower productivity, unfavorable tax regimes on importing raw materials, and other factors such as such as lack of reliable electrical supply,

From the manufacturer's perspective, there are two main drivers for the case for local manufacture. The first is market size and second is government commitment to purchase the product. As can be seen from the diagram below, where government commitment is high and a large market exists, such as Brazil, the drivers for local manufacture are strong. However in smaller countries with limited government commitment, such as Zimbabwe, the likelihood of being able to support local manufacture is low.

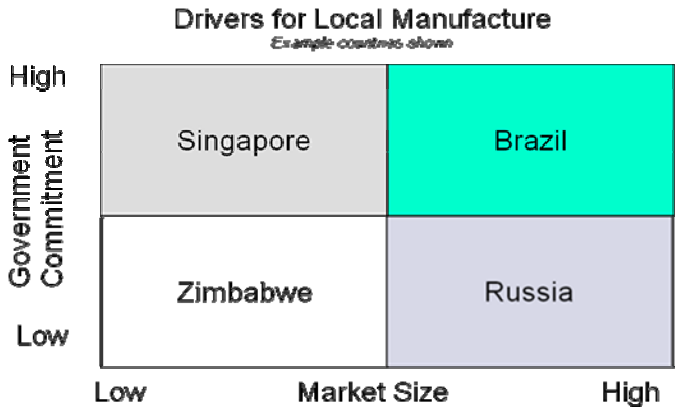

Figure 4 – Drivers for local manufacture

Several PDPs have shaped their contractual agreements to allow for engaging additional manufacturers under specific circumstances. Some PDP agreements include technology transfer procedures where the manufacturing processes are

owned and understood only by the manufacturer and not the PDP. The details of these arrangements can be an important prerequisite for later engaging additional manufacturers, and they should define

- who is responsible for managing the technology transfer
- what is the level of information to be made available to additional manufacturers
- who provides the technical help and guidance for the transfer

Recommendation

Routinely, pharmaceutical and vaccine manufacturers establish additional supply sites to increase overall supply chain capacity, to increase supply security and to lower the cost of goods by the use of low cost manufacturers. The same model should be applied to the not-for-profit model of manufacturing. PDPs should state clearly their intention to engage additional manufacturing partners, so as not to disrupt stable and collaborative corporations with the PDPs' initial manufacturing partners. Many PDPs whose products have already entered the market are concerned about the long-term commitment of their partners. Adding manufacturing organizations after products have been successfully launched and positioned, can offer long-term stability of volume and price.

Where the PDPs' partners own intellectual property (IP) or technical know-how associated with the product or its manufacture, the ability to transfer this technology to others is often constrained by the terms of the individual agreement. However, this should not stop PDPs from agreeing with their partners how the partners plan to expand their supply network to add capacity and security of supply and to lower the cost of goods.

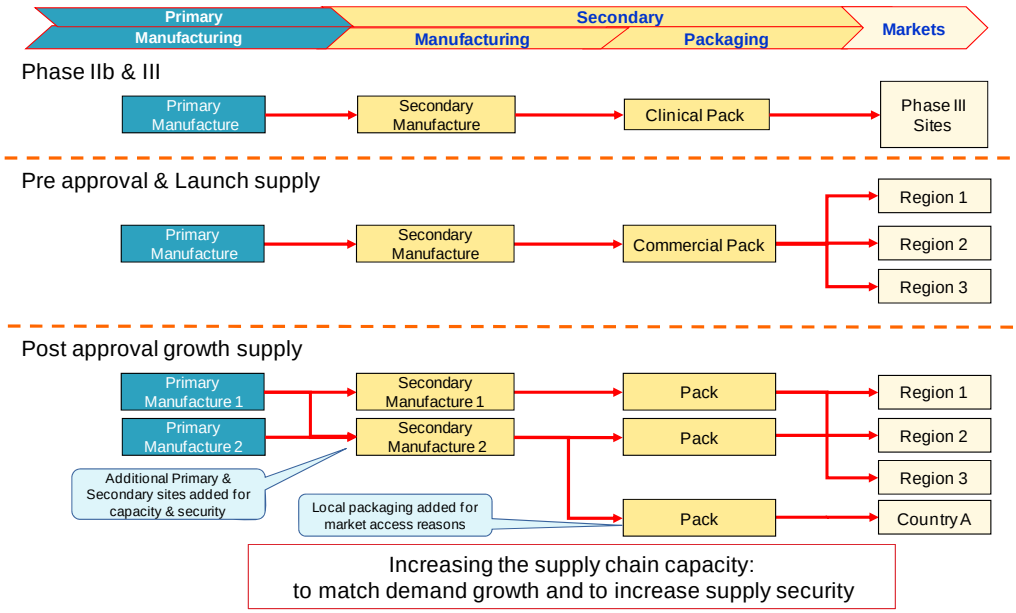

Figure 5 - Supply Chain diagram - adding additional manufacturing

When adding local manufactures specifically for market access and for local political reasons, PDPs and their partners should maintain a high level of transparency about the cost of the product available from other sources. If local manufacture is to be engaged in areas without a highly developed pharmaceutical manufacturing industry, the extent of local work should be limited where possible, to packaging operations which can be labor intensive but have limited impact on the overall cost of goods and product quality. If additional local work is required, it should be limited to secondary manufacturing operations such as tablet manufacture, and fill finishing of vaccines, rather than activities associated with drug substance manufacture and vaccine cell growth which adds significant technical complexity, and greater quality compliance risk

Examples:

AERAS

Aeras noted that a number of countries restrict the importation of bulk BCG vaccines and instead require local manufacture. Therefore, Aeras have already started discussions about establishing local manufacture with a number of established manufacturers of vaccines in China, India and Korea, who are already producing vaccines for local markets.

MMV

MMV agreements do not preclude market entry by generic manufacturers and ensure that IP issues do not adversely affect development and distribution through public sector channels in malaria-endemic countries. These agreements also allow for the technology transfer of production to third parties, if the partner is unable or unwilling to provide product for specific markets.

DNDI

In order to facilitate patients' access to treatment, DNDi facilitated and supported a South-South technology transfer between Farmanguinhos, Brazil and Cipla Ltd, India, where Farmanguinhos has been involved in the development, production and implementation of Artesunate-Mefloquine (ASMQ) FDC in Latin America while Cipla is in charge of production and distribution outside Latin America.

7. COST OF GOODS

Interview Findings:

As seen in Table 1 below, the majority of the PDPs interviewed understand their cost of goods (COGs) and set target COGs in their Target Product Profiles.

Some PDPs have undertaken willingness to pay studies, to help their partners determine the tiered prices at which public health markets and private sector markets are willing to buy their products. However, other PDPs have not established robust COGs projections or analyzed the relationship between the cost of their products and the potential uptake, despite being late in the development cycle. If PDPs do not know the actual COGs, because of complexities in the manufacturing processes or their partner's unwillingness to share the information, it is difficult to have informed discussions about product pricing.

In discussions on pricing strategies with manufacturing partners, a number of PDPs found that understanding the COGs provides good leverage in negotiating pricing. By that understanding, the PDP can determine how expensive the product might be to manufacture, and use this information in agreeing public sector selling prices.

PDP	Launched Product	Launch year	Partner	Target price in TPP	COGs determined	Willingness to pay analysis	Demand analysis	Differentiation public/private Markets
AERAS				Yes	Yes	Yes	Yes	Yes
MVI				Yes	Yes	No	Yes	No
MVP	MenAfriVac	2010	Serum Institute of India Ltd	Yes	Yes	Yes	Yes	Yes
PDVI				Yes	Yes	Yes	Yes	Yes
DNDi	ASMQ - Fixed-Dose Artesunate/Mefloquine (Malaria) ASAQ Fixed-Dose Artesunate/Amodiaquine (Malaria)	2008 2009	Farmanguinhos, Brazil / Cipla, India Sanofi Aventis/MMV	Yes	Yes	No	Yes	Yes
iOWH	Paromomycin	2007	Gland Pharma Ltd	Yes	Yes	Yes	Yes	Yes
MMV	Coartem®-*D*	2009	Novartis	Yes	Yes	No	Yes	Yes
TB Alliance				Yes	Yes	Yes	Yes	Yes
IPM				Yes	Yes	No	Yes	TBD
FIND	Liquid Culture & Drug	2007	Becton, Dickinson	Yes	Yes	Yes	Yes	Yes

	susceptibility test		and Company					
	Rapid speciation test	2007	Tauns Co. Ltd.					
	Line Probe Assey (Manual NAAT)	2008	Hain Lifescience					
	Fluorescence microscopy	2009	Carl Zeiss MicroImaging GmbH					
	Automated NAAT	2010	Cepheid					

Table 1: Cost of Goods and Demand analysis

Recommendation

See also PDP pricing discussion paper for more detail.

During development, the current COGs for a PDP's product should be calculated based on whatever production process and demand scenarios exist at the time. COGs should be re-calculated as products advance through development or whenever significant events occur that might influence projections. These recalculations should take into account revisions to forecasted demand volumes.

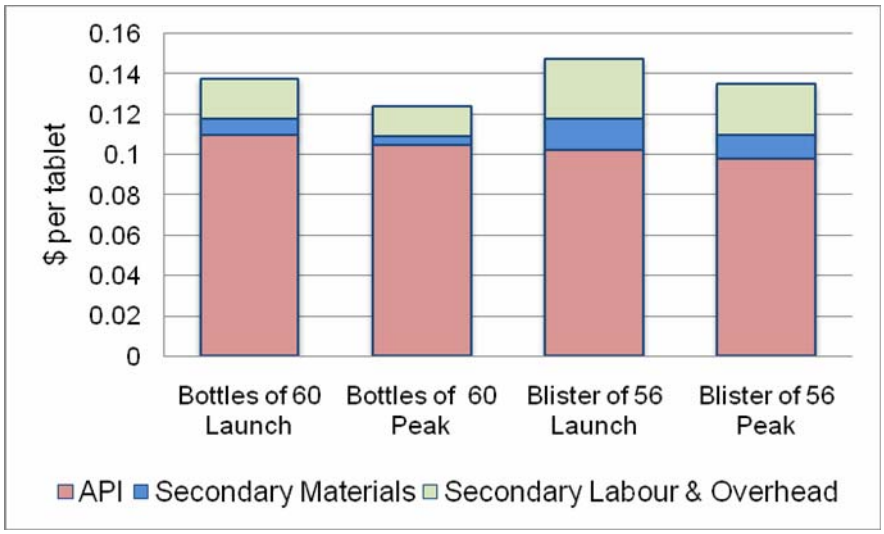

Figure 6 - Example cost of goods comparison between launch and peak demand

Understanding the potential COGs at launch and at peak demand allows PDPs and their partners to identify ways to lower costs. The figure above shows a product with a significant cost of goods challenge: The API represents the majority of the cost and does not decrease significantly as volumes increase, whereas the cost of secondary materials and labor is reduced as volume increase. Understanding cost breakdowns to this level of detail allows PDPs and their manufacturing partners to have meaningful discussions on how to reduce COGs, by

- improving process efficiencies and yields
- investigating alternative manufacturing processes
- telescoping synthesis stages
- sourcing lower cost raw materials, excipients and packaging components

Some PDPs find it difficult to estimate COGs because their manufacturing partners are unwilling to share cost information in sufficient detail to make their estimates meaningful. However, among the PDP community, and with the help of manufacturing specialists, sufficient knowledge is available to determine COGs of products manufactured and packaged using similar technology. Thus, cost projections can be modeled to validate those supplied by their partners.

Examples:

MMV

MMV builds Target COGs into their TPPs. They understand how COGs change as their products advance through development and how volume affects COGs during commercial manufacturing. They reassess the projected COGs for their products at each development stage, and they only progress products through a stage if it proves to be affordable. In identifying new malaria treatments, MMV looks for molecules with simple synthetic profiles, which allow for lower COGs.

MMV noted that projecting COGs for the five years following launch is challenging, and developing expertise in this area is not a core mandate of their mission. With that said MMV supports and will continue to support the efforts of its partners to manage COGs to the extent that MMV can make meaningful contributions. Such contributions include identifying alternative suppliers of quality API, when it helps the partners lower their COGs and investing R&D in new ways of synthesizing API (e.g., OZ 439, fully synthetic antimalarial peroxide).

FIND

FIND establishes Target COGs from the onset of a project, and COGs are routinely discussed during the development process to ensure their diagnostic tests remain affordable. They base COGs estimates on the price of comparable diagnostic tests; for new categories of diagnostic test, they use informed judgment; for example, the target COGs of the liquid culture test method were based on available data on the cost of solid culture test method.

FIND has a clear understanding of the relationship between COGs for their products and production volume, based on the experience of staff that has spent decades in the diagnostics industry. However, FIND is not in the position to make volume commitments. A number of ways to reduce the cost of instrumentation ownership have been developed:

- Instruments are leased to the users rather than sold to them
- The amortized cost of the instrumentation and service contracts is included in the cost of reagents sold to the users, based on the forecasted use of the reagents per annum.

MVP

MVP had extensive discussions with potential customers for the meningitis vaccine, to determine the maximum price they would be willing to pay. They established a target selling price of $0.50 per dose. This price was based on broad experience of working in Africa and from interactions with inter-agency coordinating committees, run by the Ministers of Health in the countries where meningitis is endemic. MVP has established a model that demonstrates the net benefit of an affordable low-cost meningitis vaccine. At a $0.50 per dose target price, which was thought to be technically achievable, the vaccine was proven affordable and would generate a net *savings* when compared to the cost of acute treatment campaigns in meningitis epidemics. Then MVP selected the technology platform and manufacturing process for their product, to ensure it could be produced for the 50¢ selling price.

8. TECHNICAL STEWARDSHIP FOR APPROVED PRODUCTS

Interview findings

The majority of PDPs rely on their manufacturing partners to develop and optimize the manufacturing processes for their products, and upon approval, most PDPs assume that the technical responsibility for the manufacturing process rests firmly with their partners, as does ensuring GMP compliance. Thus, when considering adding additional manufacturers, or the need to improve processes, some PDPs have included clauses in manufacturing contracts to ensure that their partners are responsible for providing the technical resource required for successful transfer and for process improvement.

The Concept Foundation noted that they retain the right to conduct annual GMP inspections of their partners, after product launch. Through such an inspection they determined that one of their commercial partners was no longer in GMP compliance. Concept Foundation terminated the licensing agreement with the company and transferred production elsewhere.

The extent to which the PDPs are involved in their partners' GMP compliance depends on the GMP expertise of the partner. Some PDPs take responsibility for ensuring quality of the clinical trial material through audits (AERAS), while others do not become involved at this level.

PDPs' primary concern was to select manufacturing partners that are compliant with highly regulated market GMP standards and that manufacture their products in facilities that are prequalified by WHO. PDPs noted that larger pharmaceutical partners like Novartis, Sanofi-Aventis and Pfizer are very self-sufficient and require little or no quality compliance input from PDPs; however, for some smaller low-cost companies, PDPs have provided expert assistance to establish quality managements systems for manufacturing that are compliant with stringent regulatory authorities (SRAs) and/or WHO pre-qualification.

Some PDPs recognize that their manufacturing partners are either unable or unwilling to provide the necessary technical and quality management support over the product lifecycle, so they have retained the rights of technical oversight themselves. In this situation, the PDP or its successors must maintain the vital technical competencies to support their products.

Recommendation

At the time of approval, the majority of pharmaceutical and vaccine products have not yet been manufactured in sufficient quantities to provide assurance that the processes are sufficiently robust and repeatable. Therefore, PDPs and their partners should identify the key technical challenges associated with the manufacture and the quality assurance (QA) release of their products. These challenges should be well documented and included in an assessment of the robustness of the manufacturing and analytical processes.

PDPs and their partners should further assess the resources required to support the product long term. PDPs should state very clearly in contracts that their manufacturing partners are responsible for providing technical support for the product upon approval and throughout its lifecycle.

If PDPs' partners are unable or unwilling to maintain technical support for the product over its lifecycle, as may be the case with low-cost suppliers and regional or local manufactures, then PDPs or their successor organizations must make other provisions for maintaining the technical stewardship for their products. This stewardship could become the responsibility of procuring organizations and key stakeholders such as GFATM, PEPFAR, etc. PDPs have so far found it difficult to negotiate these transitions, and this should be subject of further investigation.

Maintaining GMP quality compliance of approved products should be the responsibility of the manufacturing partner. The key to ensuring GMP compliance lies in selecting the appropriate partner, who has willingness and ability to maintain compliance within the requirements of WHO and SRAs. Where necessary, PDPs can support their partners in establishing the necessary quality management systems. However, if the partner needs help establishing or upgrading their GMP compliance, PDPs might need to assess the ability and willingness of their partner to sustain compliance once the product is approved.

Some organizations like Concept Foundation believe that they have an ongoing obligation for quality oversight of their products. PDPs need to determine who will be responsible for maintaining this role if their development partners are unable or unwilling to maintain the obligation.

Examples

FIND

When selecting a new partner, FIND conducts technical and financial due diligence audits in addition to GMP audits.

PDVI

Although PDVI does not have any responsibility for the quality compliance of vaccines developed by their partners, they do support quality compliance in an indirect way: PDVI is funding the update of WHO's manufacturing guidelines for the manufacture of dengue vaccine.

CONCEPT FOUNDATION

The Concept Foundation continues to provide technical support and quality oversight for their products, despite the fact that the products have been approved for many years. They do this because their manufacturing partners do not have the capability.

9. SUPPLY CHAIN MANAGEMENT

Interview Findings:

For PDPs that have launched products, the supply chain is generally under the control of the PDP's manufacturing partner, up to the point of entry into a country.

Responsibility for converting raw materials into finished goods always sits with the manufacturing partners, and generally, so does the management of the economic trade route. "Economic Trade Route" defines the parties accountable for purchasing and selling the product as it progresses from raw materials to finished product and, ultimately, for use by patients.

Responsibility for shipment to and importation into a specific country depends on the terms of the supply and tender agreements.

Recommendation

PDPs should establish clear responsibility for managing the supply of their products. In most cases these responsibilities are with the PDPs' manufacturing and supply partners.

The time horizon of supply chain planning is typically up to twelve to eighteen months from time of placement of the order to delivery to the warehouse. PDPs should initially ensure that their partners have the expertise to manage their supply chains over this time horizon. Further topics important in the selection of M&S partners are the capacity to manage and set stock-holding policies as well as policies that provide suitable visibility across the supply chain, to ensure supply security.

Examples:

FIND

FIND do not get involved in supply chain planning, other than in market vigilance when twice a year FIND meet with their supply partners to understand the market dynamics and agree on the forward forecasts and to review any adverse events. The supply chain up to ex-factory is managed by FIND's partners, with distribution and supply to the various markets handled by a direct partner or by global, regional and local distribution partners established with or without the help of FIND.

MVP

MVP's demand forecasts provide the Serum Institute with a forward projection of demand over a twelve-month time horizon. With this information, the Serum Institute can plan their manufacturing operations efficiently with a minimum of waste. The Serum Institute is responsible for managing the public-sector supply of MVP's vaccine, based on UNICEF tenders. The Serum Institute has experience managing similar supply chains with a number of other WHO prequalified vaccines they supply via UNICEF tenders. Private-sector sales are managed by Serum using commercial sales processes.

MMV

Factors that can impact public-sector market demand in most malaria endemic countries are

- complex financing processes involving international donor funds for procurement of malaria treatments
- lengthy approval processes
- often inefficient tender processes

These dynamics obviously present challenges for manufacturers trying to anticipate manufacturing requirements and production schedules. An additional complexity, specific to the manufacture of ACTs, is the need to source plant-extracted API (from artemisia annua), which can create lead times of nine to eighteen months, based on growing and extraction requirements.

One example of how a manufacturer has diminished the impact of market volatility of agricultural products on its finished products is the decision by MMV's partner Novartis to lock in supply commitments with API suppliers on a rolling three-year basis. While this arrangement has negative cost implications for the management of API, Novartis is willing to pay the price to ensure they can meet their public commitment to supply up to 100 million treatments per year.

10. DISTRIBUTION

Interview Findings

Most PDPs do not plan to play any active role in the distribution of their products once they are approved. Nevertheless, many feel an obligation to ensure a sustainable distribution process is in place. In most cases the partner takes on general responsibilities, including the market authorization as well as responsibility for setting up local distribution. However, there are cases when the PDP's partner is unable to support global or regional distribution. In these cases, PDPs have helped partners identify suitable distribution organizations who can assume these responsibilities.

For the majority of products made available to the public sector, in-country distribution frequently becomes the responsibility of the national governments. However, in many countries it is not simply a matter of developing and registering a product for it to be readily available to those in need. Challenges exist to distribute sufficient quantities to remote areas under suitable environmental conditions, especially if cold chain distribution is required, as is the case with many vaccines.

A number of PDPs with approved products have had to establish suitable distribution networks in country. (Refer to the MMV & MVP examples.) In many cases products can be distributed through existing channels, especially if they are to substitute for previously broadly used products, such as antimalarials or tuberculosis medicines. When the availability of a product is provided without instructions on how best to use it, issues arise. Some PDPs are concerned that in some settings (notably the private sector), guaranteeing correct use is a larger issue than product availability.

Product distribution and demand dynamics are strongly interrelated, and they need to be dealt with in conjunction and cooperation. Weaknesses on either side will negatively affect the other. Where the distribution of innovative medicines fails to reach broader populations, implementing innovative treatment strategies is difficult. On the other hand, where treatment strategies with new products are not successfully implemented into the broader medical care, demand will lag behind original projections, frustrating manufacturing and supply planning.

Where use of a product is strongly dependent on government health policies and their public implementation, the capability to reach remote or marginalized populations is more a function of the health system than the distribution network. PDPs provide countries with information so that they can decide whether to include the new product in their national healthcare system (see also the Steering Committee's paper on Country Decision Making).

Recommendations

Product distribution should be the responsibility of PDPs' partners and government agencies; the PDPs' manufacturing and supply partners should assess the national product distribution capacities. PDPs, funders and implementation agencies may have to assist local distribution systems, especially if the M&S partners are new to the national market or the technology employed requires specialist distribution such as cold chain. Where products produce a waste stream, such as used syringes or vaginal rings, PDPs may also need to assist their partners in establishing the suitable processes and means to safely destroy the waste products.

Examples

Some PDPs, although they do not intend to be responsible for distribution and supply, have put considerable effort into helping national healthcare systems to improve both their respective healthcare policies and their supply and distribution capacities.

MVP

MVP invested in strengthening the security of the MenAfriVac cold chain with help from the Dell Foundation. Funds were used to purchase vaccines, to improve the cold chain distribution and waste management systems and to collect and

destroy used needles, syringes and vials. With this money, MVP funded equipment, established processes and trained people in the collection and destruction of waste materials generated during the mass vaccination program.

FIND

Some of FIND's development partners only had experience in supplying their local markets, so FIND has helped partners to select distribution companies that can supply and provide after-sales support for their products in other countries where they will be used.

TB ALLIANCE

For the public sector, a number of international channels exist for the payment of TB drugs, including UNITAID, DFID, USAID, and the Global Fund. With funding from these sources or from national budgets, the National TB Programs procure the drugs (either from the Stop TB Partnership's Global Drug Facility or from individual manufacturers) and distribute them in country. When the TB Alliance's drugs become registered, they will be distributed in the public sector and paid for by these sources.

DNDI

As result of a collaboration between DNDi , NGOs, governments, pharmaceutical companies, and the WHO, NECT, a combination of Nifurtimox and Eflornithin, is provided free of charge for the treatment of stage II sleeping sickness. It constitutes an alternative supply model where the drugs donated by Sanofi-Aventis and Bayer Schering Pharma AG are distributed into countries by MSF logistics under WHO coordination.

CONCLUSION

Context

Manufacturing and supply planning represents a series of challenges that should be addressed at the start of development programs for innovative health goods. This is not unique to PDPs. In contrast to the classical innovative pharmaceutical company model, which typically integrates all functions and operations of product development, manufacturing and commercialization in a single organization, PDPs are, for the most part, more focused on product development. Although all are committed to access, they have only very limited in-house manufacturing, supply and marketing capacities. This model creates a unique setting where completion of development and market entry can only be accomplished in partnership with organizations that supplement PDPs' capabilities and capacities. Further to the challenge of evaluating and selecting manufacturing and supply partners for access activities, PDPs must also anticipate various aspects of manufacturing planning early in the development process, often before a competent manufacturing partner has been found.

In the interviews that informed the development of this paper, it became apparent that there is a wide range of quite different manufacturing and supply settings and models that have been or are being developed by PDPs, and they are mostly driven by the characteristics of the product and the markets they serve. Some models appear to be very robust, especially where the partnership has already been established. Those PDPs with limited experience in manufacturing issues struggle to weave manufacturing planning into development, and they often fail to attend adequately to COGs projections and demand forecasting.

Shaping the Manufacturing & Supply Strategy

Many effective ways exist to shape the manufacturing and supply architecture for products developed by PDPs. With a thorough understanding of the division of labor between PDPs and partners, PDPs are able to evaluate and select high-quality partners to provide secure supply of their product over the long term. Some PDPs deal with supply issues only as they appear, but maturing organizations allow for a more forward-looking approach.

The entry of a new product into the market usually marks the milestone where the path of not-for-profit development meets for-profit manufacturing and supply. When these paths intersect, a clear understanding of the mutual needs and expectations of both parties is a prerequisite for a long-term healthy supply relationship. Matching the not-for-profit development and the for-profit commercial worlds is easier where commercial partners have the economic depth and the corporate will to support low-cost and low-margin manufacture for the long term. In other situations where manufacturing and supply partners may not have the same financial ability and corporate willingness, PDPs have helped negotiate financial incentives to support the establishment of supply chains. This latter case, however, highlights a key finding from the

research for this paper: the need for PDPs to plan for the long-term sustainability and security of product supply, beyond the initial launch period.

Numbers matter

While the product development process often focuses on the quality of their product, quantities become center stage when planning for market introduction and a secure supply. Manufacturing capacities must be defined early, taking into account the long lead-times typically required to establish new manufacturing facilities and equipment. However good or important a product seems to be, the business case for its introduction into markets must be based on solid analysis. Will the limited resources of national healthcare systems or global funders be available for the introduction of the PDP's product?

These issues crystallize while planning for manufacturing and supply. The relationships between product price, market demand and health resources must be fully understood. Even in established markets, building reliable models for robust demand forecasts is often fraught with unknowns and difficult decisions. Because of the extra challenges to building reliable demand forecasts for many of the products, PDPs have sometimes shied away from the process. For the most part PDPs' partners cannot be relied upon to develop market forecasts on their own. Many PDPs have the depth of disease knowledge and market access understanding that together with specific regional or local market data can best establish a good understanding of global demand.

Some PDPs report difficultly understanding the true COGs for their products, when they have little experience in pricing manufacture and negotiating supply agreements. This deficiency should not stop PDPs from trying to better understand the relationship between all of the elements of cost that make up the true COGs. They should find ways among themselves to share valuable pricing experience and to seek expert help when necessary.

Although many PDPs do not want to be deeply involved in planning manufacturing capacity and supply issues, evidence shows that a good understanding of these challenges and the technology involved can be instrumental in ensuring the secure supply of low-cost quality products.

Ways forward:

As always there is so much to learn from each other, especially for those PDPs who are developing candidates with a high probability of success and limited organizational history in the manufacturing, market entry and commercialization process. PDPS should find ways to confidentially share information among themselves, about the manufacturing and supply agreements established with their partners. They also should consider the long-term stewardship of the products. Merely hoping that their manufacturing and supply partners might take on this important role does not guarantee success, especially with partners that might only be regional or local players.

The authors feel that the fragmentation of the PDPs by disease areas, infective agents and types of medicine hinders the growth and learning of their access organizations. Integrating lessons learned, the successes and failures, and developing sophisticated and reliable business partners throughout the world is difficult for a single organization. The more ground a PDP has covered in this field, the more confident and sophisticated their processes become. However, repeating this learning curve in every PDP seems expensive and difficult to accomplish.

Aware of this, the PDPs have been putting considerable effort into sharing their experiences, analyzing the challenges and seeking ways to multiply successful practices.

APPENDICES

1. Abbreviations
2. Organizations interviewed
3. Project Phases of products being developed by PDPs interviewed
4. Example PDP & Stakeholder questionnaire
5. Terms of Reference
6. Related publications and sources
7. Authors biographies

1. Table of acronyms and abbreviations

AERAS	The Aeras Global TB Vaccination Foundation
ASAQ	Artesunate/Amodiaquine fixed dose tablets
ASMQ	Artesunate/Mefloquine fixed dose tablets
BCG	Bacillus Calmette-Guérin
BD	Becton, Dickinson and Company
BMGF	Bill and Melinda Gates Foundation
CHAI	Clinton Health Access Initiative
CMC	Chemistry Manufacturing & Controls regulatory affairs
COGs	Cost of Goods
CTM	Clinical Trial Materials
DNDi	Drugs for Neglected Diseases initiative
EPI	Epidemiology
FDA	Food and Drug Administration
FIND	Foundation for Innovative Diagnostics
GAVI	Global Alliance for Vaccines and Immunization
GFATM	Global Fund for AIDS, Tuberculosis and Malaria
GMP	Good Manufacturing Practice
GSK	GlaxoSmithKline
IPM	International Partnership for Microbicides
IMS	Intercontinental Marketing Services
IND	Investigational new drug application
iOWH	Institute for OneWorld Health
KOL	Key Opinion Leader
M&S	Manufacturing and Supply
MMV	Medicines for Malaria Venture
MAH	Marketing Authorization Holder
MVI	Malaria Vaccine Initiative
MVP	Meningitis Vaccine Project
NAAT	Nucleic Acid Amplification Test
NGO	Non Governmental Organization
NIH	National Institutes of Health
PDP	Product Development Partnership
PDVI	Pediatric Dengue Vaccine Initiative
PEPFAR	U.S. President's Emergency Plan for AIDS Relief
R&D	Research & Development
SMS	Short Message Service
TB Alliance	Global Alliance for TB Drug Development
WHO	World Health Organization

2. Organizations interviewed

Type	Org.	Name	Role
Vaccines	AERAS	Rita Khanna	General Counsel
		Eric Tsao	Senior Director, Technical Operations
	MVI	Carla Botting	Director Product Development & Access
		Florence Kaltovich	Regulatory Affairs and Quality Assurance Advisor
	MVP	Marc LaForce	Director
	PDVI	Rich Mahoney	Director, Access
Medicines	Concept Foundation	Peter Hall	Chief Executive Officer
		Umberto Zardo	Senior Advisor, Quality Assurance
	DNDi	Jean-René Kiechel	Senior Pharma Advisor & Product Manager
	iOWH	Tue Nguyen	Vice President, Research & Pre-Clinical Development/Leader Diarrheal Diseases
		Debra Vallner	Visceral Leishmaniasis Team Leader
	MMV	George Jagoe	Executive Vice President, Global Access
		Joan Herbert	Business Development Manager
	TB Alliance	Elizabeth Gardiner	Vice President, Market Access
		William Wells	Director, Market Access
Microbicides	IPM	Pam Norick	Executive Vice President, External Relations
		Brid Devlin	Executive Vice President for Product Development
Diagnostics	FIND	Evan Lee	Senior Policy Officer
		Ranald Sutherland	Technology & Business Development
Stakeholder	Bill & Melinda Gates Foundation	Patricia Atkinson	Senior Program Officer
	Clinton Health Access Initiative	Inder Singh	Director, Drug Access
	WHO	Martin Howell Friede	Technical Officer, Initiative for Vaccine Research
Consultant	Consultant	Julie Milstein	Consultant, Regulatory Affairs
	TropMed Pharma	Ian Boulton	Consultant, Pricing Strategy

3. Project Phase of Products being developed by PDPs

Phase of PDPs' Products: Therapeutics

PDP	Product	Regulatory Strategy	Phase I	Phase II	Phase III	Registration	Phase IV	Launch	Partner
DNDi	NECT (Nifurtimox-Eflornithine Co-Administration)	Twinned, Article 58 for NCEs, local RA for combos of already regulated products			IIIb			2009	Epicentre & others
	ASMQ - Fixed-Dose Artesunate/Mefloquine (Malaria)						IV / Approved	2008	Farmanguinhos, Brazil / Cipla, India
	ASAQ Fixed-Dose Artesunate/Amodiaquine (Malaria)						IV / Approved	2007	Sanofi Aventis/MMV
	Combination Therapy (VL in Asia)				III			2011	Indian Medical Research Council & others
	Combination Therapy (VL in Latin America)				III			2012	Brazilian Ministry of Health
	Combination Therapy (VL in Africa)				III			2010	Kenya Medical Research Institute & others
	Fexinidazole (HAT)							2014	Sanofi-Aventis
	Azoles E!224 (Chagas)			II				2015	Eisai
	Paediatic benznidazole							2011	Pharmaceutical Laboratory of Pernambuco State (LAFEPE), Brazil
iOWH	Paromomycin						IV / Approved in India, approval pending in Bangladesh and Nepal	2007	Gland Pharma Ltd
	Synthetic Artemisinin	Alternative API Manufacturing process						2012	Amyris Biotechnologies / Sanofi Aventis
MMV	Coartem®-*D*	SRAs with / without WHO PQ					IV / Approved	2009	Novartis
	ASAQ Winthrop						IV / Approved	2007	Sanofi Aventis/DNDi
	Eurartesim™					Registration			sigma-tau
	Pyramax®	Article 58				Registration			Shin Poong/ University of Iowa
	IV artesunate					Registration			Guilin
	AZCQ				III				Pfizer
	Arterolane/PQP			?					Ranbaxy
TB Alliance	Moxifloxacin	SRAs with / without WHO PQ		II	III	2014			Bayer
	PA-824			II				TBD	Novartis
	TMC-207			II				TBD	Tibotec

Phase of PDPs' Products: Diagnostics

PDP	Product	Regulatory Strategy	Development	Evaluation	Endorsement	Launch	Partner
FIND	Liquid Culture & Drug susceptibility test	WHO endorsement				2007	Becton, Dickinson and Company
	Rapid speciation test					2007	Tauns Co. Ltd.
	Line Probe Assay (Manual NAAT)					2008	Hain Lifescience
	Fluorescence microscopy					2009	Carl Zeiss MicroImaging GmbH
	Automated NAAT					2010	Cepheid
	LAMP Assay (Manual NAAT)			Evaluation		2011	Eiken Chemical Company
	Uinary antigen detection		Development			2012	
	Antibody detection test (1st generation)		Development			2013	
	Rapid colorimetric DST (TLA)		Development			2015	
	POC NAAT detection		Development			2015	

Phase of PDPs' Products: Vaccines

PDP	Product	Regulatory Strategy	Phase I	Phase II	Phase III	Registration	Phase IV	Launch	Partner
AERAS	MVA85A / AERAS-485	SRA joint review, WHO PQ		IIb				2014	Oxford University
	AERAS-402 / Crucell Ad35			IIb				2015	Crucell
	GSK M72			II				2017	GSK
	SSI HyVac4 / AERAS-404		I						Statens Serum Institut
	AERAS-422 (rBCG)		I						Aeras
MVI	GSK (RTS, S/AS01)	Article 58, joint review by AVAREF, WHO PQ			III			2015 - 2016	GSK
MVP	MenAfriVac	Local RA, twinned review, joint review, WHO, PQ					IV / Approved	2010	Serum Institute of India Ltd
PDVI	WRAIR	SRA joint review, WHO PQ		II					GSK
	Acambis			IIb					Sanofi Pasteur
	U.S. NIH Dengue vaccine		I						Biological E, Butantan, Panacea & Vabiotech
	InViragen		I						Inviragen
	Hawaii Biotech		I						Hawaii Biotech/Merck

Phase of PDPs Products: Preventative Microbicides

PDP	Product	Regulatory Strategy	Phase I	Phase II	Phase III	Registration	Phase IV	Launch	Partner
IPM	Dapivirine Vaginal Ring			I/II					QPharma

PDP MANUFACTURING AND SUPPLY STRATEGY REVIEW QUESTIONS

There are 13 Manufacturing Strategy Question Subject areas. These questions seek to understand the PDPs' manufacturing approaches and strategies and in particular how they are planning the secure supply of quality products at affordable prices once their products have received regulatory approval.

As you will note, the questions are designed with a series of follow-on questions that explore the subject area in more detail. The follow-on questions asked during the interview will depend on the PDP's products and their responsibility for manufacturing and supply.

One hour is allocated to the telephone questionnaire, which might mean that discussion of some topics listed must be constrained to ensure the overall questionnaire is completed during the call.

Interviewee Information

Name of the PDP:
Date:
Names of the person / people interviewed:
Role:
Emails:
Interviewers: **Nick Davies & Thomas Mertenskötter**

Product	Regulatory Strategy	Phase II	Phase III	Registration	Phase IV	Launch	Partner

1. **Organizational design**

    a. Who will manufacture the products that you will market?

    b. Will the manufacturer of your products also be the market authorization holder?

    c. Have you formally developed a manufacturing strategy and has this been endorsed by you and your manufacturing partner's (partners') governance boards?

    d. Who in your PDP is responsible for managing the relationship with the organization that will manufacture and supply your products to market?

    e. Do you anticipate this organizational design will change over time?

2. **Product launch plans**

    a. Are your products NCEs, or already approved products with a new indication?

        i. If it's a new indication of an existing product, are they available as generic products?

    b. How many countries do you anticipate will untimely launch your products?

c. Will your product be supplied on a public tender basis?

d. Will they also be supplied to the private market?

3. Understanding Demand

a. Who is responsible for modeling the anticipated demand for your products?

b. Have product demand forecasts been developed?

   i. How have these forecasts been modeled?

   ii. What level of accuracy would you put on these forecasts?

   iii. Has a baseline forecast plus upside and downside forecasts been established?

c. Do you understand the key drivers that influence demand?

d. Have you been able to assign demand by pack/strength/country/region etc?

   i. Are you/your partners able to calculate drug product/drug substance demand from these forecasts?

   ii. How far out do the forecasts go post market approval (6mths, 1 year, 5 years, 10 years)?

e. What time buckets are the forecasts calculated in (yearly/ quarterly / monthly)?

4. Understanding Capacity

a. Do you anticipate that process batch sizes will have to be increased prior to product launch?

b. Does your manufacturing process require specialized/ dedicated manufacturing equipment?

c. Have you developed a capacity model showing how capacity will need to increase over time?

a. Do you have an understanding of how your manufacturing and supplier capacities are aligned with the projected demand for your products?

d. Do you understand the lead times required to bring new manufacturing capacity on line

e. Who will pay for increases in capacity?

5. Additional Manufacturing and Supply Partners

b. Have you established any dual/multiple sourcing policies?

c. Do you intend to roll out supply to local/national manufacturing sites?

   i. If so how will these be selected and managed?

d. Have you considered if local manufacture is required for market access reasons?

   i. How is this best achieved?

   ii. What will be the decision process to determine at what stage in the manufacturing process local manufacture will be conducted?

   iii. How will the financial impact of this decision be determined?

e. Do you intend to ensure generic manufacturers get licenses to manufacture and market your products?

   i. If so how will this be managed?

ii. Will rights be limited to specific countries/markets?

6. Target Cost of Goods?

a. Have you established target co**s**t of goods based on what the customer will pay?

i. Were COGs part of the TPP?

ii. Are these targets segmented by customer group?

b. Do you know your current COGs?

i. If so how was this calculated, what is included in the cost?

c. Have you projected what the COGs will be at launch and say 5 years post launch?

ii. How is this related to volume?

d. Have you identified ways to reduce the COGs?

i. Process efficiencies?

ii. Alternative manufacturing processes?

iii. Lowering cost of raw materials/excipients/packaging components etc?

iv. Low cost sources of supply?

7. Manufacturing and Supply contracts?

a. What are the key contractual terms you establish with your manufacturing and supply partners?

b. Do your contracts allow your Pharma partners to make a profit? How is the margin allowed determined?

c. Do your contracts encourage cost savings and if so how are these savings shared by the parties to the contract?

8. Quality Compliance

a. What will the role of the PDP be in ensuring GMP compliance of supplied product?

i. What role do you anticipate in the future?

b. What role does your PDP play in the release of product?

ii. How will this role change over time?

9. Manufacturing Process

a. What are the key technical challenges to the manufacture of your products?

b. How robust do you anticipate your manufacturing and analytical processes to be at the time of regulatory submission?

c. Do you anticipate any significant process robustness and repeatability issues that need to be resolved prior to final approval and launch?

d. How easy do you anticipate it will be to transfer your process to other manufacturing sites?

i. What level of technical support do you anticipate tech transfer will require?

ii. Who will provide this support?

e. What do you anticipate your PDP's role will be in providing technical support and oversight to the manufacturing process during the products life cycle?

i. When do you see this role transitioning to others?

f. What level of technical competence do you anticipate will be required to routinely manufacture your products following successful tech transfer?

10. Supply Chain Planning

a. What's the anticipated role of your PDP in managing the supply of products to patients?

i. How will this role change over time?

b. How will manufacturing and supply partners understand and manage the demand?

c. How long does it take for raw materials to be converted into finished product?

d. What lead times are required to manage the production process?

e. What visibility of stock levels across the supply chain do you anticipate?

f. Have stock holding levels been established and who manages the supply chain?

g. Have key performance indicators (KPI's) been established to monitor the manufacture and supply of your products?

h. How is supply chain security assessed to ensure continuity of supply?

11. Economic Trade Route (How products are bought and sold as it progresses from raw materials to finished product and ultimately use by the patient

a. Who buys the raw materials your product is made from?

b. Who pays for the materials to be converted into finished products?

c. Who pays for the finished products, if it different to b?

d. Who pays for the finished product to be distributed to patients?

e. Who pays for the finished product to be used by patients?

f. How will this be different for public and private sales?

g. Who will manage and have oversight to these trade routes?

h. What do you see as the major risks to these trade routes?

12. Distribution & Logistics

a. Who will manage the logistics and distribution of your products to the end users?

b. How will this differ for public and private markets?

c. What role will your PDP have in establishing this capability?

d. Have you identified logistics and distribution providers who can support this activity?

e. Will your product require cold chain or controlled condition storage and shipment?

    i. If so how confident are you that suitable storage and transportation conditions can be maintained throughout the logistics and distribution process?

f. Who will provide oversight to the distribution and logistics processes?

    g. Have you been able to determine the cost of distribution and logistics?

13. Anything else to consider?

a. Is there anything else the PDP considers important in establishing their manufacturing strategy?

PDP MANUFACTURING AND SUPPLY STRATEGY STAKEHOLDER QUESTIONS

Interviewee Information

Name of the Stakeholder:
Date:
Names of the person / people interviewed:
Roles:
Emails: mailto:
Interviewers: **Nick Davies & Thomas Mertenskötter**

Development Partnerships (PDPs), on "PDP Manufacturing and Supply Strategies". This paper is looking at the various approaches that PDPs are using to ensure the secure supply of quality product once their products have received regulatory approval.

As a key stakeholder in the work of the PDPs, Thomas Mertenskoetter and I would like to schedule a teleconference with yourself and whomever else you think appropriate to discuss the following:

1. What do you think are the most important elements for PDPs to take into account when planning their manufacturing and supply approaches?
2. Are you confident that the PDPs approaches to ensuring secure supply of quality products are appropriate for the current development stage of their products?
3. What, if anything else, should they be doing to establish secure supply of their products for the longer term?
4. Do you anticipate that the Clinton Health Access Initiative will have a role in manufacturing and supply of PDP products?
5. How well do you believe the potential demand for the PDPs products is understood?
6. Based on your experience, do you have a view on appropriate target cost of goods for the PDP's products?
7. Selecting and adding manufacturing & supply partners;
    a. Do you believe PDPs should have dual/multiple sourcing for approved products? Why?
    b. Do you believe PDPs should be identifying and working with local/national manufacturing partners or is that someone else's responsibility?
    c. If local manufacture is to be established, how do you believe this is best achieved?
    d. Do you believe generic manufacturers should be given licenses to manufacture and market PDP's products?
8. What role do you anticipate the PDPs will have in managing the ongoing supply of their products?

5. Terms of Reference

CHALLENGES IN ENSURING EQUITABLE ACCESS TO NEW HEALTH PRODUCTS IN LOW INCOME COUNTRIES – CROSS-PDP ANALYSIS AND DISCUSSION PAPERS

Context

Product development partnerships (PDPs) and their donors have recognized that ensuring access to new products is a complex and, in many ways, uncharted challenge. Creating access to new products requires PDPs to track, develop and manage a wide range of information and partnerships at both country-specific and global levels. As no single PDP has the in-house expertise and capacity in all areas of access, an exchange of information and ideas across PDPs is recognized as a useful and efficient way to improve the effectiveness of the PDPs.

Individuals working on access at PDPs are involved in a concerted effort to exchange information and have established a Steering Committee, co-chaired by the Malaria Vaccine Initiative (MVI) and the Global Alliance for TB Drug Development (TB Alliance), and comprised of these two organizations plus the International Partnerships for Microbicides, Foundation for Innovative New Diagnostics, Aeras, Medicines for Malaria Venture, Pediatric Dengue Vaccine Initiative, Institute for OneWorld Health, Drugs for Neglected Diseases initiative and Innovative Vector Control Consortium; the Concept Foundation serves as secretariat to the group.

To date, there have been several PDP discussions[1] which have helped to elaborate key issues and have fostered strong collaboration across the PDPs.

Several topics have emerged that the Steering Committee would like to develop into a series of discussion papers on key access issues facing PDPs. Owing to time and work constraints, the Steering Committee will engage consultants to work on the discussion papers in collaboration with individual PDP access staff members.

Objectives

The overall goal is to enhance the effectiveness and efficiencies of PDP and to contribute to the knowledge base of PDP access work. The purpose of the discussion papers is to explore and document PDP experiences and challenges with regard to access, with an emphasis on documenting the different strategies taken by various PDPs and the accompanying rationales.

Strategy and outputs

We anticipate that the project will produce up to eight discussion papers (see below for the list of topics and first draft of possible questions to be answered). The papers should be succinct 5-6 page documents, although additional data or annexes may be necessary. The primary audience is PDPs and donors but the papers would also be shared with other stakeholders and interested parties such as MSF, the Clinton Foundation and others.

The output documents are intended to act as a reference for PDPs' own, future efforts – as a kind of "how to" manual. They cannot, however, be prescriptive, given that strategic choices differ by modality (vaccines, drugs, diagnostics, and insecticides), disease, product and competitor product/intervention characteristics, and other factors. Instead, they will outline the range of strategies devised by different PDPs and the reasons why individual PDPs believed (at the time) that these strategies were the most effective (a) in general or (b) for their particular situation.

[1] These discussions include a September 2008 PDP Access meeting in Geneva, the BCG-led PDP design team work for the July 2009 BMGF PDP forum in Seattle, a PDP Access meeting in Divonne, France in July 2010, and ongoing PDP Access Steering Committee teleconferences.

To avoid the natural tendency to focus only on the positive outcomes rather than an open discussion of the issues, these are not intended as “best practice” studies. For a number of questions there may be no satisfactory answer; these can be highlighted at the end of each document. Other issues may be better addressed via detailed studies or existing white papers – a limited number of these can be cited or suggested as future activities. The current documents should be practical, have a coherent logic, and move beyond the realm of bullet points.

In addition to the draft and final discussion papers, the consultants are also expected to forward interview notes to the relevant project advisor on an ongoing basis (see below).

Roles and responsibilities.

The PDP Access Steering Committee will maintain general oversight of the project. The TB Alliance will manage the project funds and the contracting of the consultants on behalf of the Steering Committee. For each discussion paper topic, a consultant will manage the logistics and writing, including the summarizing of previous input (e.g., from the previous discussions and forums mentioned above), scheduling and conduct of interviews, typing up interview notes, writing of the first draft, and revisions and edits. The consultant will help to ensure uniformity of presentation, timeliness of delivery and unbiased narratives for the discussion papers. PDP volunteers (i.e. access staff, 1-3 per topic) will act as project advisors – they will help the consultant to select interviewees and hone the key issues (including additions or edits to the interview questions below); these volunteers will also act as co-interviewers, and read and revise first drafts. Core interviewees and Steering Committee members will then provide feedback and edits to the draft papers, which will be incorporated by the consultant.

Individual consultants may propose to work on one, or more than one, of the topics listed below.

Several, but not all, PDPs would be expected to be interviewed for each topic, resulting in a document that can blend experiences to protect confidentiality concerns (especially regarding particular IP and pricing strategies) and that also reflects the complexity of the topics. In consultation with the PDP leads, the consultant may also interview external stakeholders (including donors, country stakeholders etc.), but it is anticipated that this would be limited in number and the primary focus on response will be the PDPs themselves.

It will be important to capture the reasoning behind different approaches for the various problems confronting PDPs. Without becoming encyclopedic, discussion papers should address any notable differences in strategy between modalities (vaccines, drugs, diagnostics, and insecticides) and diseases; they should not address only one of these areas to the exclusion of others.

6. Related publications and sources

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Dr Julie Milstien, Montpellier, France, WHO paper:
Landscape Analysis: WHO's Role in Supporting Emerging Vaccine Manufacturers, Promoting the availability and affordability of high quality vaccines of public health priority
http://www.who.int/immunization/sage/1_Final_landscape_analysis_Milstien_19_October_2010.pdf

Warren A. Kaplana and Richard Laing
Health, Nutrition and Population (HNP) Discussion Paper
LOCAL PRODUCTION: INDUSTRIAL POLICY AND ACCESS TO MEDICINES
An Overview of Key Concepts, Issues, and Opportunities for Future Research
http://www.who.int/medicines/technical_briefing/tbs/KaplanLocalProductionFinal5b15d.pdf

Brooks AD, WA Wells, TD McLean, R Khanna, R Coghlan T Mertenskoetter, LA Privor-Dumm, A Krattiger and RT Mahoney. 2010. Ensuring that Developing Countries have Access to New Healthcare Products: The Role of Product Development Partnerships. InnovationStrategy Today 3:1-5. www.biodevelopments.org/innovation/index.htm

PDP Pricing Discussion Paper
Prepared by Ian Boulton (TropMed Pharma Consulting) based on interviews conducted by Yvette Madrid on behalf of the PDP Access Steering Committee, which is made up of the following organisations: Aeras, Concept, DNDi, FIND, iOWH, IPM, IVCC, MMV, MVI, PDVI, and TB Alliance.
http://www.conceptfoundation.org/files/Pricing Discussion Paper.pdf

PDP Regulatory Discussion Paper
Prepared by Julie Milstien (consultant) and Mike Brennan (Aeras), on behalf of the PDP Access Steering Committee, which is made up of the following organizations: Aeras, Concept, DNDi, FIND, iOWH, IPM, IVCC, MMV, PATH MVI, PDVI, and TB Alliance.
http://www.conceptfoundation.org/files/PDP%20Regulatory%20Discussion%20Paper.pdf

PDP Access Strategy Discussion Paper
Prepared by Laura Herman (FSG), Amanda Oudin (FSG), Elizabeth Gardiner (TB Alliance), Florence Camus-Bablon (DNDi), and Don Douglas (PDVI), on behalf of the PDP Access Steering Committee, which is made up of the following organizations: Aeras, Concept (Secretariat), DNDi, FIND, iOWH, IPM, IVCC, MMV, MVI, PATH, PDVI, and TB Alliance.
http://www.conceptfoundation.org/files/PDP%20Access%20Strategy%20Discussion%20Paper.pdf

PDP Support of Country Decision Making: A Discussion Paper
Prepared by William Wells (TB Alliance) and Alan Brooks (PATH Malaria Vaccine Initiative), with interviewing assistance from Eric-Marie Dupuy, on behalf of the PDP Access Steering Committee, which is made up of the following organizations: Aeras, Concept, DNDi, FIND, iOWH, IPM, IVCC, MMV, MVI, PDVI, and TB Alliance.
http://www.conceptfoundation.org/files/PDP%20Country%20Decision%20Making%20Discussion%20Paper.pdf

PDVI Occasional Paper 5: The manufacturing and supply of dengue vaccine
Don Frances, Don Douglas & Richard Mahoney. Dec 2010.
http://www.pdvi.org/documents/PDVI_Occasional_Paper_5.pdf

Forecasting dengue vaccine demand in disease endemic and non-endemic countries
Ananda Amarasinghe, Ole Wichmann, Harold S. Margolis and Richard T. Mahoney
Pediatric Dengue Vaccine Initiative (PDVI); International Vaccine Institute; Seoul, Korea
The Human Vaccine journal. September 2010
http://www.landesbioscience.com/journals/vaccines/AmarasingheHV6-9.pdf

IAVI Policy Discussion Paper
Speeding the Manufacture of an HIV Vaccine
Saul Walker, Dr. Jane Rowley and Dr. Robert Hecht. January 2005
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DFID Health Systems Resource Centre, Issues Paper
Processes and Issues for Improving Access to Medicines.
The evidence base for domestic production and greater access to Medicines.
Jean-Marc Guimier, Evan Lee and Michel Grupper. September 2004. http://www.hlsp.org/LinkClick.aspx?fileticket=-wnRCJ0AhQs%3D&tabid=1643

7. Authors' Biographies

Nick C Davies

CEO & PRINCIPAL CONSULTANT NDA CONSULTANTS

Nick is a Senior Consultant with 26+ years of delivering results with global pharmaceutical manufacturing leaders such as GlaxoSmithKline, and The International Partnership for Microbicides.

In 2009 Nick formed NDA Consultants with a number of former GSK colleagues. NDA is an international consultancy which delivers innovative solutions globally to the pharmaceutical and biotech industries.

Nicks' expertise lies in manufacturing strategy and rationalization, strategic sourcing and outsourcing, global supply chain start-ups and leadership, new product introduction, technology transfer, and complex global change program leadership. He has established and started up new manufacturing facilities globally, rationalized global manufacturing operations, and closed and sold manufacturing facilities.

During his time with GSK Nick had responsibility for the annual supply of over $5billion worth of pharmaceutical product globally, and lead new product introductions.

Nick has lived in 5 different countries (UK, Thailand, South Korea, USA, and Canada), and conducted business in more than 26 countries including China, India, Thailand, Korea, Singapore, Kenya, Brazil, and Argentina.

Nick received a M.Sc. in Design of Production Systems from Loughborough University of Technology, UK, and a B.Sc. in Engineering Science from the University of Warwick, UK.

He is a Fédération Européenne d'Association Nationales d'Ingénieus European Engineer, and an Engineering Council of the U.K Chartered Engineer.

Nick has a Lean Sigma Green Belt, and is a Member of; the Institute of Measurement and Control, the Institute of Engineering and Technology, the International Society of Pharmaceutical Engineers, and the Project Management Institute.

Nick lives in Raleigh NC USA with his wife and two children.

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Thomas Mertenskoetter

Thomas has worked for 20 years in the field of infectious diseases, in clinical care and drug development, as well as engaging in commercialization and access planning. 2010 Thomas founded T.O.M. Life Science Consulting, offering specialized Medical Affairs and R&D services for the Pharmaceutical Industry, Biotech and Global Health Programs

In 1992 he received his Medical Doctorate degree from the University of Hamburg and his training in Tropical Medicine and Parasitology from the Bernhard-Nocht-Institute. He served as infectious diseases physician at University Hospital Hamburg Eppendorf and at the Institute for Tropical Medicine, where he engaged in the clinical care of HIV/AIDS, tropical medicine and other infectious diseases, as well as in the clinical development of new antivirals.

Thomas joined GlaxoWellcome in 1997 where held several positions within Medical Affairs, first with GW Germany then as a Director of Medical Communications within the Global HIV R&D Team of GSK in the UK.

In 2002 Thomas moved to Gilead Sciences Germany as the Director of Medical Affairs where he was responsible for the development and implementation of Gilead's clinical research program in the fields of HIV and viral hepatitis and internal and external medical communications and operations.

Joining the International Partnership for Microbicides in 2007 as Executive Director External Relations Europe he led IPM's overall resource development engagement in Europe building support for the development of new technologies for HIV prevention. He coordinated relationships with European donors, Civil Society partners, and academia and industry partners. He was member of the Dapivirine Microbicide Product Development Team and led the research and planning related to access to microbicides.

Over the years, Thomas has contributed to various public-private research programs focusing on the epidemiology of HIV and AIDS, observational research in HIV care, HIV therapy pharmacovigilance and the development and introduction of HIV prevention tools for developing countries.

Thomas is member of the International AIDS Society (IAS) and the European Association for the Study of the Liver (EASL).

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