

Timing Access: A Study of PDP Access Activities and Timelines

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Abstract

The Product Development Partnership (PDP) Access Steering Committee commissioned this paper to explore the optimal timing and sequencing of access-related activities for drugs and vaccines, the underlying rationale for this sequencing, and the dependencies between activities. The paper accompanies two generic Gantt charts—one for drugs and one for vaccines—that capture the timing and sequencing of access activities. Semi-structured telephone interviews were conducted with sixteen respondents in donor organizations, pharmaceutical companies with experience of drug and vaccine development and commercialization in low- and middle-income countries (LMICs), and PDPs working on drug and vaccine projects.

The time period prior to stringent regulatory authority (SRA) or twinned product approval is referred to as “upstream” within the paper. The earliest access activities, which begin prior to Phase 2b trials, usually between nine and ten years prior to product approval by an SRA, are conducted to establish the disease context, the intellectual property context, and the key relationships with regulators and key opinion leaders that will be required throughout the following years. The second phase of upstream activities runs from between nine and six years prior to SRA product approval and occurs in parallel with Phase 2b clinical studies. These activities focus on gaining a better understanding of the value proposition of the new intervention and establishing draft strategies in areas such as regulatory affairs, manufacturing, and financing. In the period between six and three years prior to SRA product approval, around the same time that Phase 3 studies are being carried out, there are four groups of access activities for PDP consideration, which focus on building a stronger constituency of support at the global and national level and at financing agencies. Market and stakeholder studies can also continue during this time and be used as part of the relationship-building approach. In the final upstream time period from three years prior to SRA product approval, the PDP provides necessary support to manufacturing partners to ensure that the product will be ready for shipment by the time of launch in the first wave of countries. In addition, PDPs

¹ Prepared by Laura Frost, Sybil Eng, and Beth Anne Pratt (consultants) and Lois Privor-Dumm (IVAC) and William Wells (TB Alliance), on behalf of the PDP Access Steering Committee, which is made up of the following organizations: Aeras, Concept, DNDi, FIND, IAVI, iOWH, IPM, IVAC, IVCC, MMV, MVI, PDVI, and TB Alliance.

and their partners will engage in various financing activities, file an SRA regulatory package, and establish and/or refine an evidence package for both country decision makers and WHO.

In the downstream period, which refers to the time after a product receives approval from an SRA or via a twinned regulatory filing, the PDP's role becomes less active and one of supporting, informing, and building capacity for existing country-level decision-making and implementation processes. PDPs and their partners file WHO prequalification and endemic country dossiers, provide support to country policy review and pilot/demonstration studies, and support the conduct of monitoring and evaluation activities.

These timelines reveal a progression from initial scoping of value proposition and strategy, through early engagement and collection of evidence, to an intensification of engagement and assembly of evidence into formal packages to support global and country decision making, and finally to more variable involvement in roll-out and surveillance activities. This discussion paper highlights those activities identified by stakeholders as taking longer than anticipated (including manufacturing, registration, adoption, and financing issues) and causing delays (including inaccurate demand forecasts, failure to anticipate post-marketing commitments, and inability to obtain intellectual property clearance). The paper also points to some key tactics that, if implemented appropriately and in a timely manner, have the potential to accelerate access timelines (such as early country studies, financing scoping, and consultations with regulators). These considerations, plus the sample timelines, may be used by PDPs and their partners to plan access activities in a way that minimizes delays and maximizes impact.

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1. Introduction to the study

Product development partnerships (PDPs) support the development and delivery of new products aimed at alleviating the burden of disease in low- and middle-income countries (LMICs). While public-private partnerships for the innovation of new drugs and vaccines have been in existence for decades, in recent years global interest in these partnerships has been growing. New institutional models, financing mechanisms, and policy windows have emerged, allowing PDPs to proliferate and enlarge their scope.²

As PDP portfolios expand and as products enter late-stage development, PDPs and their donors have turned their attention to the issue of access. From a PDP's perspective, access refers to "a coordinated set of activities needed to ensure that products developed will ultimately have an equitable public health impact."³ To achieve this impact and ensure optimal uptake in target populations, PDPs must identify and coordinate a complex combination of information, activities, and partnerships. These activities span both global and national levels, and involve an array of stakeholders, such as pharmaceutical companies, ministries of health, planning and other government institutions in LMICs, researchers, technical agencies, financing bodies, development partners, politicians, community leaders, NGOs, and regulatory authorities. In recognition of the complexity of this task, several PDPs came together in 2008 to create the PDP Access Steering Committee⁴ as a forum to share information about how PDPs can help to ensure access to new products.

One critical area identified by the Committee was the issue of PDP access timelines. What is the relative sequencing of access activities? How might the time between the start of a product's clinical development and its implementation at the end user-level be condensed, and uptake timelines for the product optimized? When do PDP senior management teams need to start working intensively on particular access topics? The Committee commissioned the current project to research access activity timelines and to study: a) the series of activities necessary to ensure a new product reaches the end user in LMICs; b) which of these activities are more or less time sensitive; c) which later activities are dependent on earlier activities; d) which activities tend to be left until too late; and e) where and how timelines can be compressed.

The project objective was to create sample timelines for drugs and vaccines to describe the different sets of activities required and their relative timing. These sample timelines are for products—drugs and vaccines—rather than organizations and are in the form of Gantt charts, which are a type of bar chart used to illustrate a project schedule. Gantt charts plot various project activities and milestones (significant events or achievements within the project), on a

² Buse K. and Walt G. (2000). Global public-private partnerships: part II – what are the health issues for global governance? *Bulletin of the World Health Organization*, **78** (5), 699-709.

³ Brooks A.D. et al. 2010. Ensuring that developing countries have access to healthcare products: the role of product development partnerships. *Innovative Strategy Today*, **3**, 2.

⁴ <http://pdpassess.org/home>.

vertical axis against time on a horizontal axis. This type of chart allows the viewer to observe the relative start and finish dates of project lifespan activities, those activities that can be done in parallel and those that are conducted sequentially, and any activities that may be dependent on one another. The second project objective was to explain the rationale behind the timing and sequencing of the activities in the Gantt chart in a referenced discussion paper. This analysis will support PDPs in their preparations to address access issues in a logical order that does not slow down the introduction of their products.

2. Methodology

Sixteen semi-structured interviews with stakeholders from PDPs, pharmaceutical companies, and PDP donors were carried out. Respondents were chosen using purposive sampling based on an initial list of 22 stakeholders provided by the Committee. Out of these 22 potential interviewees, 16 stakeholders agreed to participate, representing the following categories: Donor (N = 3), Pharmaceutical company with experience of drug development and commercialization in LMICs (N = 4), Pharmaceutical company with experience of vaccine development and commercialization in LMICs (N = 5), PDPs working on drug projects (N = 2), and PDPs working on vaccine projects (N = 2).⁵ The Gantt chart for vaccines was also reviewed by members of the Decade of Vaccines Access working group.⁶ See Appendix I for a list of individuals and organizations interviewed.

Interviews were conducted by phone and involved a two-step process. First, respondents were provided with an initial, example Gantt timeline and Powerpoint presentation of product access activities. Access activities and milestones on the example Gantt charts are organized into the eleven categories in Table 1. These categories and access activities/milestones were generated from an initial list provided by the PDP Access Steering Committee⁷ and other materials on access.⁸ Phase 2b and pivotal Phase 3 clinical trials are included on the Gantt chart in Category 1 to show sequencing of access activities in relation to these clinical development activities, but the timing of other clinical development activities are omitted as these are already well established.

⁵ In the text, we identify respondents using codes that maintain confidentiality but provide the reader with a sense of the perspective of the particular respondent. In these codes, “DON” indicates a donor respondent, while “PHAR” and “PDP” indicate pharmaceutical and PDP respondents respectively. The code “V” refers to a respondent that works on vaccine projects while “D” refers to a person that works on drugs.

⁶ Sandy Wrobel and Carol Marzetta of Applied Strategies.

⁷ This initial list was based in part on an existing, but confidential, TB Alliance timeline, and on the Table formulated and published previously by the Steering Committee (see http://pdpaccess.org/downloads/shared/IST3_1_Brooks%20et%20al.pdf).

⁸ Frost, L. & Reich, M. 2008. *Access: how do good health technologies get to poor people in poor countries?* Cambridge, MA: Harvard Center for Population and Development.

Table 1: Categories of PDP access activities

1: Clinical	7: Economics and Financing
2: Strategy and Planning	8: Global Policy
3: Intellectual Property Management	9: Country Decision Support
4: Process Development, Manufacturing, and Supply	10: Country Implementation
5: Regulatory	11: Monitoring and Evaluation
6: Communications and Advocacy	

Second, with the example timeline as a starting point, interviews proceeded sequentially through discussion of those product access activity categories with which interviewees had the most experience, using five guiding questions:

1. Does the list and sequence of activities within each category reflect what you know to be happening now, in the projects with which you are familiar?
2. Which of the activities on the list do you view as more time sensitive? Less time sensitive? Why?
3. What access activities tend to be/have been left until too late? Or implemented too early? Why? What have been the consequences of getting timing and sequencing wrong?
4. Where and how can access timelines be compressed?
5. Is the timing of any of the activities, or the transitions between them, unduly optimistic or unrealistic? Which ones and why?

Interviews ended with respondents sharing their “big picture” ideas about how access timelines in their projects were materially impacted by specific activities or events.

The researchers took notes during the interview and provided these notes to the respondent for review. Respondents were given the opportunity to amend the notes and to control the way in which the data would be used in the project deliverables by marking the notes with the following codes: a) information can only be used as context/background; b) information cannot be used at all; and c) information can be used freely. The interviews were then analyzed thematically using codes based on pre-existing categories from the example timeline. The research protocol was reviewed by the Johns Hopkins Bloomberg School of Public Health IRB who determined that the project is “not human subjects research” and could proceed without further IRB review.

Despite certain challenges with interviewing on such a broad set of topics (see Discussion section below), it was possible to use the interview data to modify the initial, example Gantt

charts. The revised Gantt charts for drugs and vaccines are presented in Appendix II. In these charts, Year 0 is the point in the timeline when marketing authorization is received for a drug or vaccine from a stringent or twinned regulatory filing (Milestone 5.4). The starting point of the Gantt charts is Year -9.5, a timepoint that is generally prior to the start of Phase 2b clinical trials. The timeline assumes that the PDP has already established an initial target product profile (TPP) (although it may not be publicly available), that the product is likely to meet the TPP characteristics, and that the PDP has put in place policies and procedures for governing any relevant partnership with pharmaceutical companies by the time the Gantt chart begins. The timeline also assumes that Phase 2/2b studies take 2.5 years to complete, that pivotal Phase 3 studies take five years to complete, and that a SRA or twinned approval for marketing authorization will be issued 18 months following the end of pivotal Phase 3 studies⁹.

For the purposes of this paper, it is assumed that there is a single lead product candidate selected to move forward in development. All activities prior to Year 0 are considered “upstream activities” and all activities following this timepoint are called “downstream activities.” The Gantt charts include only those PDP access activities that are discrete and/or time sensitive; a longer list of access activities for PDP consideration is in Appendix III. The black arrows between activities on the Gantt chart show dependencies, specifically the prerequisite and follow-on activities for each access activity on the timeline.¹⁰

3. Findings

3.1 Upstream Activities on the Sample Gantt Charts, Year -9.5 to Year 0

3.1.1 Upstream Activities: Year -9.5

The starting point of the Gantt charts is Year -9.5, six months prior to the start of Phase 2/2b clinical trials. On both the drug and vaccine Gantt charts, there are four activities to consider at this early point.¹¹ These activities establish the disease context, the intellectual property context, and the key relationships with regulators and key opinion leaders that will be required throughout the following years.

Activity 2.1: Assess Burden of Disease and Unmet Need

The first is an activity to **assess the burden (incidence and prevalence) of disease and unmet need (Activity 2.1)**. This activity could take a minimal amount of effort if the disease is well-

⁹ Some PDPs are going to national regulatory authorities (NRAs) for first approval and this may have implications for timing and pathways. See pages 21-22 for details.

¹⁰ A detailed list and description of these dependencies is provided in a separate document at <http://pdaccess.org/home>.

¹¹ This sub-section describes the first four activities on the Gantt chart, while later sub-sections refer to “activity groups” that are sets of activities on the Gantt chart.

characterized and existing data are available, or several years if disease surveillance systems need to be put in place. If burden of disease data are not readily available or likely underestimate disease burden in the opinion of disease experts, the activity may need to start even earlier than Year -9.5 and be updated periodically, so it captures any changes in disease epidemiology that may occur as the PDP approaches Year 0. One respondent noted that raw data and any statistical models used to generate estimates must be as accurate and current as possible to avoid a disconnect between product supply and actual product need (PHAR-V). Experts also must endorse the methodologies used to generate estimates to avoid problems down the road where estimates are not considered useful. At the same time, estimates of disease burden and unmet need must be derived at the project start because the data are needed for revising the TPP in Year -9 (Activity 2.2). The TPP requires information on the epidemiology of disease to show that there is a public health rationale for the product. This activity also feeds directly into developing the first strategic demand forecast for global supply in Year -8 (Activity 4.1) because, for the forecast to be accurate, it must take into account unmet medical need and current burden of disease. Finally, the activity links to a financing activity on the vaccine Gantt chart that begins in Year -6: Presenting the investment case and conducting funding discussions with GAVI (where relevant) (Activity 7.4V). Investment cases for GAVI include information important for vaccine decision-making such as potential lives saved by the vaccine, illness averted, and economic impact. Even if there is not a GAVI investment case, establishing burden of disease and the potential impact of a product are generally important activities to conduct as early as possible.

Activity 3.1: Develop Intellectual Property Map

The second access activity at Year -9.5 is to **develop an IP map and ensure IP clearance from patent holders (Activity 3.1)**. This activity begins with a short process (six months or less) and involves developing a map that identifies all of the IP clearances that will be required to proceed with development and access activities. The IP map can aid a PDP in determining potential IP barriers and needs to be developed in Year -9.5 for two reasons: 1) so PDPs can ensure IP clearance from patent holders as they move forward in the timeline, and 2) so these IP considerations can be part of negotiations in initial agreements with manufacturing partners (Activity 4.3). These negotiations with manufacturers begin as early as Year -7 (see below). Ensuring IP clearance from patent holders is iterative from Year -9.5 until all production agreements with manufacturing partners are complete. Two interview respondents noted that a robust approach to this activity is particularly important for vaccine projects, where multistep processes for production may require numerous IP clearances from many different institutions (PHAR-V; PDP-V).

Activity 5.1: Confer with Regulatory Agencies

Conferring with regulatory agencies (Activity 5.1) is the third activity a PDP should consider at Year -9.5. SRAs¹² will typically be the regulators that PDPs interact with initially and these agencies provide guidance for formal meetings between product sponsors and regulatory

¹² PDPs may be working with one or two stringent regulatory authorities at one time.

agency staff that take place at specific time points in product development.¹³ The meetings are likely to be even more important in those areas where there have been few or no clinical trials conducted in a modern regulatory environment, as is the case for many of the areas of interest to the PDPs. Such new areas may require the stringent regulator to convene expert panels and draft new guidances, which can be a time-consuming process.

Discussions with regulatory authorities in these early meetings focus primarily on clinical trial issues such as adequacy of preclinical data, clinical trial design including endpoints, establishing correlates of protection, appropriate cohorts to study, safety issues of potential concern, and regulatory submission requirements. These discussions also have relevance to access activities. First, discussions with regulatory agencies early in product development will inform the product's regulatory strategy (Activity 2.4) and regulatory filing (Activity 5.3). Second, gaining mutual agreement in a timely fashion as the development program proceeds can avoid costly and time-consuming attempts at correction later in the process, which would have the effect of delaying product access. Third, these discussions between PDPs and regulators allow both parties to agree on those safety issues that need further follow-up via post-marketing surveillance and studies, and to determine who would be responsible. This, in turn, will enable PDPs to support partners in: a) developing a plan for post-marketing surveillance that is acceptable to regulators (Activity 5.2); and b) carrying out these surveillance activities (Activity 11.2). Fourth, early meetings with regulators may involve discussions of manufacturing plans. For vaccines in particular, any improvement of the manufacturing process also requires regulatory approval, which may result in time delays unless negotiated early (PHAR-V). Process improvement can be cost prohibitive or time prohibitive depending on the amount of information required by regulators (PHAR-V).

Activity 6.1: Key Opinion Leaders and Expert Groups

The final access activity at Year -9.5 is **identification of global medical and scientific key opinion leaders (KOLs)—global, regional, and national leaders—to serve on expert groups (Activity 6.1)**. Examples are the Pneumococcal Awareness Council of Experts (PACE) and DNDi's platforms for neglected diseases. These expert bodies are particularly important to assemble early for novel products and neglected disease areas where groups of experts have not yet come together to meet on a regular basis.¹⁴ The experts in these groups are distinct from national-level public health officials, who are engaged later in the access timeline (see Activity 9.2 below). The initial identification of these medical and scientific experts may be a short-term

¹³ These time points for the United States Food and Drug Administration include: a) just prior to submission of an investigational new drug application; b) at the end of Phase 1; c) at the end of Phase 2b (Year -6.5); and d) just before submission of a new drug application/biologics licensing application (between Year -1 and Year -1.5). See U.S. Department of Health and Human Services, Center for Drug Evaluation and Research (CDER)/Center for Biologics Evaluation and Research (CBER). 2009. *Guidance for Industry: Formal Meetings between the FDA and Sponsors or Applicants*. Available from:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.

¹⁴ For more examples and further discussion, see Wells, W & Brooks, A. 2011. Adoption of new health products in low and middle income settings: how product development partnerships can support country decision making. *Health Research Policy and Systems*, 9(15). Available from: <http://www.health-policy-systems.com/content/9/1/15>.

(six-month) activity, but the activities of the expert group are ongoing throughout the access timeline, potentially extending from the beginning of the Gantt chart (Year -9.5) through to the time of product approval (Milestone 5.4 at Year 0) if the experts will be involved in country decision support activities (see Activity 9.2 below). One respondent noted that the expert groups need to be established at this early point because it takes time for the group to develop a voice and have an impact on both upstream and downstream access activities (PDP-V).

Expert groups link to a range of access activities and provide:

- Important stakeholder feedback on revised TPPs (Activity 2.2), indicating whether or not the TPP makes sense given their knowledge of burden of disease and unmet need (PHAR-V);
- Expert advice for product discussions with regulators (Activity 5.1) (PHAR-D);
- Powerful knowledge building and advocacy with donors (Activity 7.1). One respondent stated that product funding from donors could not be secured without these critical product champions and indicated that if it wasn't possible to find a group of experts supportive of a particular development project, PDPs might want to focus their efforts on other projects instead (PHAR-V).
- Input during consultations with WHO regarding the product information to be submitted to its expert committees (STAG or SAGE) (Activity 8.1);
- Ideas for publication planning (Activity 6.2); and
- Product advocacy in countries (Activity 9.2).

3.1.2 Upstream Activities: Year -9 to Year -6

The second phase of upstream activities runs from Year -9 to Year -6, and occurs at the same time as Phase 2b clinical studies. Four groups of activities take place within this timeframe. These activities focus on gaining a better understanding of the value proposition of the new intervention and establishing draft strategies in areas such as regulatory affairs, manufacturing, and financing.

Activity Group: TPP Revision

The first is **revising the TPP and obtaining stakeholder feedback (Activity 2.2)**. The initial revision may be a short-term (six-month) activity but it is iterative as PDPs move forward, with the TPP being refined at specific decision points as new information about the product becomes available. The TPP is usually finalized around the time that decisions are being made to proceed to Phase 3 clinical studies. TPP revisions at this later stage will primarily affect products still in development or focus on packaging implications such as package or vial size (these decisions may impact timing because even changes in packaging must be tested). The TPP will ideally contain target populations, general pricing statements, and information about product presentation, dosage form and schedule, expected efficacy, temperature considerations, shelf-life, and stability since these are variables that will determine whether the product will successfully gain access to LMIC markets (PHAR-V, DON, and DON).

In some projects, the TPP can also specify product price. For example, the price for MenAfriVac, the vaccine against group A meningococcus, was defined as US\$0.50 per dose from the beginning of the project. This was based on extensive pre-existing knowledge about the technical requirements (not always available for products) and consultations with Ministers of Health in the meningitis belt as to an affordable price (PHAR-V; PHAR-V). This example is an exception, however. Generally price is determined through negotiation, and may be based on volumes and how competitive the bidding process is. Optimization of the cost of process development and manufacturing will typically be very important for most PDPs, akin to the emphasis that a generic manufacturer would put on price and process optimization. For vaccines, prices are often set once the procurement process starts. For GAVI eligible countries and PAHO countries, prices are generally set prior to application for GAVI funding or through an annual bid process for PAHO.

A TPP for a vaccine will include information on target formulation, which will allow PDPs to determine the impact that any formulation constraints¹⁵ may have on demand for the product in target LMIC markets (Activity 2.3V). These two activities—revising the TPP (Activity 2.2) and **assessing impact of potential formulation constraints on demand (Activity 2.3V)** therefore occur in close sequence on the vaccine Gantt at Years -9.0 and -8.5, respectively. Since an early demand forecast is a necessary component of an investment case for GAVI funding, the TPP also indirectly affects the investment case activity for vaccines (Activity 7.4V; see below). The components of formulation and dosing included in the TPP will also influence determination of the product's ultimate price in the public sector.

Respondents in both drug and vaccine projects emphasized the importance of gaining stakeholder feedback and buy-in on the TPP revision and subsequent iterations. The expert groups, mentioned previously and established in Activity 6.1, can provide this feedback. Another respondent gained this feedback through a specific TPP meeting with stakeholders to pressure test various aspects of acceptability (PDP-V). This painstaking work on the TPP (which may at times require additional market research) and continuous feedback on revisions from stakeholders can result in time savings in that potential stakeholder concerns can be anticipated and worked through before the new product is considered for adoption.

Activity Group: Landscaping and Strategic Planning

The second group of activities that occur in the Year -9 to Year -6 period involves assessing the landscape and creating strategies¹⁶ in the areas of regulatory,¹⁷ current and future market for

¹⁵ For example, whether a vaccine will require refrigeration, and whether it will require mixing of components or will be ready-to-use.

¹⁶ Herman, L., Oudin, A., Gardiner, E., Camus-Bablon, F., & Douglas, D. PDP Access Strategy Discussion Paper. Available from: <http://pdpaccess.org/downloads/projects/full-papers/PDP%20Access%20Strategy%20Discussion%20Paper.pdf>.

¹⁷ Milstein, J & Brennan, M. 2010. PDP Regulatory Discussion Paper. October 2010. Available from: <http://pdpaccess.org/downloads/projects/full-papers/PDP%20Regulatory%20Discussion%20Paper.pdf>.

the product, financing,¹⁸ pricing,¹⁹ and policy. These are all initially six-month activities but will require less activity if participants are already familiar with the relevant global health actors and policies. Assessments and strategies are revised as new information becomes available. They start early because they trigger a set of downstream activities.

The first of these downstream activities, at Year -9, is **defining regulatory strategy (Activity 2.4)**. Several respondents emphasized that an iterative approach to regulatory strategy is central to access timelines and that failure to undertake it properly, starting in Year -9, has the potential for causing delays to product availability. According to one respondent's experience, PDP partners often underestimate the clout and impact that regulatory authorities have on critical issues including manufacturing site, required documentation for regulatory filings, and number and types of pre-clinical and clinical studies required (PHAR-D). Tactics to minimize delays include a robust regulatory strategy and ongoing dialogue with regulators.

The initial regulatory strategy is built from the issues discussed with regulators in Year -9.5 (Activity 5.1; see above). The specific timing for updating the strategy will vary between, for example, novel products versus reformulations or a change of production processes. In a later iteration of the regulatory strategy, around Year -7.5, refinements should include a list of priority countries for filing and product rollout. This list is derived via a circular process involving the product rollout strategy and the strategic demand forecast. The **product rollout strategy (Activity 2.7)** at Year -7.5 defines the countries in which the PDP will introduce the product sequentially. The strategic demand forecast (Activity 4.1; discussed in more detail below) is initially built from:

- Burden of disease assessment (Activity 2.1);
- Market research (Activity 2.5);
- Any early, available data on financing and pricing (Activity 2.6); and
- Initial product rollout strategy (Activity 2.7).

The product rollout strategy as noted is one input into data calculations for the strategic demand forecast and the resulting data outputs circle back to influence refinements to the rollout strategy. This then leads to assessment of both registration and adoption requirements in specific countries and, iteratively, modifications to the regulatory strategy.

Developing the regulatory and rollout strategies early on is important as it will feed into the development of supply, manufacturing, and financing strategies. For manufacturing, certain of the priority countries from the rollout strategy may require national production, but that must be checked against the regulatory requirements of SRAs to have production at plants that have met their approval upon inspection. The financing needs and capabilities of countries in the

¹⁸ Jones, A., & Privor-Dumm, L. PDP Economics and Financing Discussion Paper. Available from: <http://pdpassess.org/downloads/projects/full-papers/PDP%20Economics%20and%20Financing%20Paper.pdf>.

¹⁹ Boulton, I. PDP Pricing Discussion Paper. Available from: <http://pdpassess.org/downloads/projects/full-papers/PDP%20Pricing%20Paper.pdf>.

rollout strategy will also have to be assessed in deriving the **financing, pricing, and policy assessments and strategies (Activity 2.6)** at Year -7.5. Another input into these strategies is the market research mentioned above for Year -8 (Establish likely market demand and market landscape at time of product launch (Activity 2.5)), as market landscaping should include any information or predictions on innovative financing mechanisms that may be in place when the product is launched, possible competitor products, and trends in policy (such as changes to GAVI co-payment policies). This market research is an iterative activity that involves discussions with regional and national stakeholders, as well as environmental scanning and researching of the market (including standards of care), both with respect to what the market looks like at the current time and what it is likely to look like once the product is introduced.

One pharmaceutical respondent pointed out that pricing assessment and strategy (part of the broader Activity 2.6 at Year -7.5) will furthermore feed back into modifications of the regulatory strategy developed for a product (PHAR-D). If tiered pricing will be used for a product, his company first files for product approval in those countries where the product will have a higher price before filing in those where it will have a lower price, as countries with pending approvals will frequently reference the prices in other countries where the product is already approved. There are of course exceptions to this filing sequence. For life-saving vaccines and drugs, there is increased effort to reduce the delays in introduction time between high- and low-income countries. There has even been one recent example, that of rotavirus vaccine, where filing was in a middle-income country prior to high-income countries and there was also a push to introduce quickly in low-income countries.

In contrast to the pharmaceutical respondent just cited, another study has found PDP respondents unwilling to commit to early pricing discussions, thinking it “better to keep [pricing] options open (within broad affordability parameters) to keep partners engaged and work with them to refine the pricing over the course of the development process”²⁰ PDPs, the author argued, wished “to keep their options open for as long as possible during the development process...this reflects the lack of case histories for many PDPs to fall back on in dealing with the complexities of pricing negotiations with private sector partners. It also reflects the uncertainties inherent in the early stage of product development that their projects are currently at.”²¹

Activity Group: Manufacturing for Product Supply

The third group of activities that occurs between Year -9 and Year -6 relate to manufacturing for product supply. Occurring at Year -7.5 is the first high-level **strategic demand forecast for global supply (Activity 4.1;** mentioned above). Strategic demand forecasting is an iterative activity; one respondent suggested the forecast should be updated semi-annually (PDP-V). The forecast connects to preparation of a GAVI investment case (Activity 7.6 on the vaccine Gantt;

²⁰ Boulton, I. 2010. PDP Pricing Discussion Paper. October 2010. Available from: <http://pdpassess.org/downloads/projects/full-papers/PDP%20Pricing%20Paper.pdf>.

²¹ Ibid, p. 2.

relevant for those vaccine projects seeking GAVI funding) because the amount of product to be manufactured needs to be included in the request for funding.

The strategic demand forecast feeds into the **evaluation of possible manufacturing processes (including need for any capital expenses) and the assessment of a range of possible manufacturing partners and feasibility of technology transfer (if relevant) (Activity 4.2)**. This is because the demand forecast dictates the amount of product that will need to be manufactured and therefore suggests the types of manufacturing processes required for scale-up and potential partners able to carry out these processes. Activity 4.2 is a six-month activity starting at Year -7. This starts just after the first strategic demand forecast is developed and is influenced by regulatory strategy and, for vaccines, formulation decisions that would affect the viability of technology transfer (see above). Not all manufacturers may have the technical resources required to produce a complex vaccine or the capacity to formulate the product to the scale needed post-licensure.

For vaccines, manufacturing partners capable of producing marketed product are ideally identified prior to pivotal Phase 3 studies so that they can also produce product for these Phase 3 trials (PHAR-V). This eliminates the time delays in access that would be introduced by the need to transfer manufacturing “know-how” from the Phase 3 manufacturer to a different market product manufacturer. The time for these knowledge transfers can be lengthy if the manufacturing process is particularly complex, as it often is for vaccines. Any capital expenses (for example, the building of a new manufacturing plant) that emerge from the assessment in Activity 4.2 will feed into discussions about financing strategies, as discussed below. The timings mentioned in this paragraph may also be relevant for many drug projects (for the original manufacturer of product, not additional manufacturers in other regions) where it is preferable but not essential for the manufacturers of the Phase 3 product and marketed product to be the same. If the manufacturers are different, an estimated six months will be added to the timeline for bioequivalence studies with the new manufacturer’s product. Following the assessment in Activity 4.2 is the **negotiation and finalization of agreements with manufacturing partners, including agreements for technology transfer (if relevant) (Activity 4.3)**. This activity ends at Year -6.5, just prior to the initiation of pivotal Phase 3 studies.

Activity Group: Financing

The final group of activities for this upstream phase involves financing concerns. One of these activities is **knowledge building and advocacy activities with key global financing bodies (Activity 7.1)** such as the Global Drug Facility, UNITAID, GAVI, PAHO, and GFATM. Respondents involved in both drug and vaccine projects felt that the knowledge building and advocacy should begin as early as possible (although it is dependent on the product and the value proposition) because these activities take time and “it is essential to ensure that a pot is in place to pay for the product by the time it is launched” (PHAR-V). In cases where products are already funded through GFATM, this activity may not be necessary. For those cases where this activity is needed, a PDP should target the organizations identified in the earlier assessment of the financing landscape in Year -7.5 (Activity 2.6; see above). KOLs serving on product expert

groups (Activity 6.1, see above) can assist PDPs in these knowledge building and advocacy activities. As we will discuss below (see Activity 7.4), the more detailed financing discussions typically occur later, between Year-6 and Year-3, once Phase 2b data are available.

A second financing activity is **conducting funding discussions for innovative financing (Activity 7.2)**. For vaccine projects requiring innovative financing, discussions could occur as early as Year -7 after the assessment of capital expenditure needs for manufacturing partners (Activity 4.2, see above) and run for years. Seeking innovative funding at this early stage is an important tactic in accelerating timelines. In the case of the pneumococcal vaccine, PDP donors and partners focused on increasing manufacturing capacity by using an Advanced Market Commitment to mitigate the risk for companies in developing their manufacturing processes and producing the vaccine (PDP-V). This mechanism ensured that sufficient product would be available (Milestone 4.6) to meet the demand created by the PDP's advocacy and demand generation efforts at global, regional, and national levels. One respondent pointed out, "the more innovative the financing tool is, the earlier the discussions should start in the timeline" (PDP-V). In her experience with an innovative financing mechanism, she had initially assumed that the financing would be available two to three years earlier than it actually was. She warned that this activity may take longer than many people expect.

3.1.3 Upstream Activities: Year -6 to Year -3

In this time period, there are four groups of access activities for PDP consideration. These activities focus on building a stronger constituency of support at the global and national level and at financing agencies. Market and stakeholder studies can also continue during this time and be used as part of the relationship building approach.

Activity Group: Communications and Advocacy

The first group of activities relates to communications and advocacy. Starting along with pivotal Phase 3 clinical trials at Year -6, and continuing through to Year -4 is the **development of a product publication plan, identification of additional product champions, and conduct of product awareness and demand generation activities (Activity 6.2)**. For vaccines, PDPs need to ensure that interim Phase 3 clinical trial data about their product reaches the public and regulatory agencies in a timely and transparent manner. This is most efficiently done through an established publication plan (PHAR-V) which includes not only details about intended peer-reviewed publications, but also plans for relevant conference presentations and symposia. Disseminating compelling clinical trial data into the public domain can build anticipation and enthusiasm for a product at the global and national levels, accelerating access.

An activity at Year -3.5 is the work that takes place around **coalition-building at the country, regional, and/or global levels (Activity 6.4)**, which is particularly important for those products in a disease space where there already may be more than one way to treat or prevent the disease (PDP-V). Coalition building is needed so there isn't competition between these multiple

solutions and so that stakeholders plan for implications for the health system and advocate for needed investments. Depending on country planning cycles, this activity may need to start earlier to ensure the product is part of multi-year plans. It can make use of the KOL group assembled at Year -9.5 (Activity 6.1) as product advocates and may also use data from market research (Activity 2.5) and economics and financing studies (Activity 7.3) to bolster the case for the product. The need for this coalition-building activity varies depending on the nature of the product, with greater need if the public health case is less clear and there is no public fear surrounding the disease. The impact of these coalition-building activities may be to speed access, since there may be less resistance from Ministries of Health to adopt the product (Milestones 10.3 and 10.5) once local groups have endorsed it.

Activity Group: Economics and Financing

The second group of activities relates to economics and financing. Starting in Year -6, PDPs should consider **commissioning economics and financing studies (Activity 7.3)**, although neither the timing nor the requirements of funders and countries are entirely clear in this area. In general, this activity includes cost-effectiveness studies and studies of the broader economic and societal impact of a product. Cost-effectiveness studies at Year -6 will be preliminary and should be revised once pivotal Phase 3 data are available.²² The PDP can use these studies as supporting tools during funding discussions occurring concurrently (see below). These studies can also be used in coalition-building activities at the country, regional, and global levels (Activity 6.4).

A second financing activity involves **conducting funding discussions with key global financing bodies and national governments (Activity 7.4)**. These discussions also begin in Year -6, once Phase 2b data are available. Funding discussions primarily aim to establish funding streams for product procurement if relevant (in most cases, applications will be submitted to donors for procurement by countries themselves, but this is only possible if the funding stream is established and available). These discussions follow on from knowledge building and advocacy activities with key global financing bodies (Activity 7.1, see above). PDPs may not need to engage in this activity if the product is a technology with clear funding mechanisms in place. One drug PDP respondent said that her organization is instead involved in larger policy discussions on innovative financing mechanisms for new products rather than focused specifically on financing for her organization's products (PDP-D).

For vaccines, a third financing activity that can begin as early as Year -6 is a critical one if financing is being sought from GAVI: **Present investment case and conduct funding discussions with GAVI (Activity 7.4V)**. This begins briefly with presentation of the investment case to GAVI, followed by one year of funding discussions. As mentioned previously, the investment case includes information from the assessment of burden of disease and unmet need (Activity 2.1), market research (Activity 2.5), the revised TPP (Activity 2.2), and the first iteration of the

²² Jones, A. & Privor-Dumm, L. (2010). PDP Economics and Financing Discussion Paper. October 2010. Available from: <http://pdpaccess.org/downloads/projects/full-papers/PDP%20Economics%20and%20Financing%20Paper.pdf>.

strategic demand forecast (Activity 4.1). The sequencing of the investment case in relation to other activities varies. For example, negotiations with PAHO in Activity 7.4 (see above) may begin first and then influence GAVI, or they may occur at the same time.

Activity Group: Regulatory Filings

The third group of activities in this time period involves regulatory filings. Starting at Year -4, PDPs can use information from meetings with regulatory agencies (Activity 5.1) as well as emerging safety data from clinical trials to **develop plans for post-marketing surveillance (Activity 5.2)**, including acquisition of any data that allow for interpretation of potential product safety signals representing incidence above expected background rates within the patient population. This activity should be iterative. Reliable and acceptable background rates of adverse events (AE) in drug- or vaccine-unexposed individuals are critical to the interpretation of AE data that may come in amongst drug- or vaccine-exposed individuals. One respondent suggested that studies to elicit background rates in instances where data is not readily available need to be established at least two years prior to product launch (PDP-V). Another respondent noted that post-marketing commitments in the form of long-term safety studies are increasingly required by regulators. PDPs can save themselves time if they anticipate and assist partners in proactively developing studies with regulators ahead of time (PHAR-V). This plan will determine which studies need to be conducted post-licensure (Activity 11.1).

Activity Group: Country Decision Support and Country Implementation

The fourth group involves two key activities that support country decision-making and country implementation. These both start at Year -4 and last approximately two years. The first activity is **defining key issues for and against introduction in particular countries (Activity 9.1)**. Assessment of these key issues will have already been started in Year -9, as part of obtaining stakeholder feedback on the TPP (Activity 2.2), market research (Activity 2.5), and planning product rollout strategy (Activity 2.7). In Year -4, more in-depth analysis at the country level can identify specific historical, socio-cultural, economic, and political barriers to introduction (countries to focus on are determined by the product rollout strategy). A parallel activity for drug projects at Year -4 is **country studies on the target market's patients and healthcare providers (Activity 10.2D)**. These country studies provide key information required for product packaging and for informational materials targeted to healthcare providers. This activity is particularly relevant to novel drugs that rely on providers and end-users for uptake and use.

These preliminary country-specific studies (Activities 9.1 and 10.2D) should ideally be completed prior to:

- Engaging in more intensive communication with key decision makers in countries at Year -2 and onwards (Activity 9.2), as the study results will establish a more compelling case for stakeholders; and

- Submission of regulatory dossiers in the country (Activity 5.7), as the results will inform the product packaging and product insert information submitted as part of the product dossiers for marketing approval.

3.1.4 Upstream Activities: Year -3 to Year 0

In this final upstream time period, the PDP needs to support the manufacturing partner in product testing, process development, and packaging in compliance with Good Manufacturing Practices (see **Activities 4.4 and 4.5**) in order to have **product ready for shipment (Milestone 4.6)** by launch in the first wave of countries in Year 1 (Activity 10.4). In this time period, additional access activities for PDP consideration include the filing of an SRA regulatory package, the establishment and refinement of an evidence package for both country decision makers and WHO, and economics and financing activities.

Activity Group: Communications and Advocacy

First is a consideration of what the **standard evidence package will look like on a local, global, and donor level (Activity 6.3)**. It is important for this packet to evolve as new data are made available. Phase 3 data will be incorporated as they become available near the end of Year -2 (Activity 1.2). The packet will be informed by the KOL group brought together before Phase 2b (Activity 6.1, commencing at Year -9.5), since key stakeholders can provide feedback to ensure that the evidence package will be useful and compelling to local decision-makers and donors. The evidence package will also incorporate any information from ongoing dialogue between PDPs and regulatory agencies (Activity 5.1, ongoing from Year -9.5), since this may provide useful information on elements of the product development program that make the strongest arguments for product approval. The evidence package will be useful for meetings between PDPs and country decision makers (Activity 9.2, ongoing from Year -2), with the package initially informing these decision-makers about the product's value. Insights gleaned from decision-makers can be then added to the package, since these individuals will know what information makes the strongest case for product uptake and adoption in their countries. For products entering a less well-defined disease space, building of the evidence packet will take more time and require greater resources than products entering an established disease space, since data on burden of disease may not be readily available. Once the evidence package is assembled, it can be used to influence adoption by Ministries of Health (Milestones 10.3 and 10.5).

Activity Group: Regulatory

The second group of activities involves regulatory filings. Beginning in Year -2, the one-year long activity of **preparing and filing for licensure by the SRA or twinned regulatory review (Activity 5.3)** will make use of data from pivotal Phase 3 trials and will be informed by the regulatory submission requirements elaborated through ongoing dialogue with regulators (Activity 5.1). **SRA or twinned marketing authorization approval (Milestone 5.4)** is expected to take

approximately one year and triggers the filing of WHO prequalification dossiers (Activity 5.5) and endemic country dossiers (Activity 5.7) (as discussed below).

Activity Group: Global Policy

The third group of activities between Year -3 and Year 0 involves **global policy** work. In Year -8.5, the PDP will have started conducting an iterative policy landscaping activity that identified what evidence would be needed for global, regional, and national adoption of the product, and strategies to shape policy at these levels. After Year -3, the PDP can then begin **consultations with WHO on what information should be submitted to its expert committee (Activity 8.1)**—the Strategic and Technical Advisory Group (STAG) for drugs and the Strategic Advisory Group of Experts (SAGE) for vaccines. It may be necessary to start this process earlier when there has been no similar product in the past and when products will be licensed first in low-income countries. These consultations lead to the **submission of evidence to the WHO expert committee (Activity 8.2)** at Year -1, ending in the milestone of **WHO recommendation of the product (8.3)** just after Year 0 when SRA approval is received (Milestone 5.4). It should be noted that this timing is an ideal case and that there is currently a lack of clarity over whether consideration of evidence by WHO expert committees can run in parallel to SRA regulatory processes, or whether SRA approval is required first. Flowing directly from the WHO recommendation is inclusion in WHO’s standard treatment guidelines if this is relevant to the product. These policy activities at WHO are essential for novel technologies because WHO expert committees will not have reviewed them previously and because WHO recommendations are a key factor as to whether or not a LMIC decides to adopt the product. Respondents pointed out that other global organizations can influence policy, depending on the type of product and disease area: examples included GAVI, UNICEF, and UNAIDS. Regional bodies, medical societies, and global expert groups (Activity 6.1; see above) can also influence global policy through endorsements and calls to action (PDP-V).

For novel technologies not already on the **global Essential Medicines List (WHO EML; Activity 8.4)**, PDPs can apply for inclusion after gaining stringent regulatory approval for the product (Activity 5.4). Respondents pointed out that having a product on the WHO EML does not trigger country decision-making (see below) but the absence of a product on the list can delay adoption within some countries. For example, one person recounted, “We approached WHO to see if we could apply for the drug to be on the essential drugs list. WHO said there was no reason for the essential drug list to be updated because the class of drugs was already approved on the list. This delayed roll out in some countries because at the country level, there is a narrow interpretation of the global essential drugs list. Countries didn’t see the drug on the global list so were less willing to put it on their national lists. This meant that the company had to spend resources and time on lobbying in some countries through on-the-ground local stakeholders or product advocates” (PHAR-D). Inclusion on the WHO EML and on WHO standard treatment guidelines facilitate country policy review activities downstream (Activity 10.2) because countries are unlikely to place the product on the national EML or the national treatment guidelines if they are not already on the global list and guidelines.

Activity Group: Country Decision Support and Country Implementation

The fourth group of activities involves supporting countries with decision-making about product adoption and country implementation. At Year -2, PDPs are able to begin **engaging in intensive communication with key country-level decision-makers (Activity 9.2)**. This involves intensive dialogue and updates with in-country public health officials including national program managers, regulatory authorities, WHO country office staff, Ministry of Finance staff, and local researchers and academics. In many countries, communication will be through issue-specific technical working groups (TWGs) or committees within the Ministry of Health that help to make technical decisions about products, coordinate activities, and allocate roles. Members of the KOL expert group (Activity 6.1) can be influential in conversations with country-level decision-makers, particularly if they have been carefully selected for their expertise in these regions. For some PDPs, it may be more financially and programmatically efficient to engage with decision-makers at the regional level (at conferences, for example). Intensive engagement with decision-makers at the country level, however, will be necessary for novel technologies and for those countries with deep concerns about a particular new product (as identified in Activity 9.1, see above). One PDP respondent pointed out that intensive country-level engagement needs to be carefully and strategically considered as it is not possible to engage every country at this level of decision-making (PDP-D).²³ Another respondent (donor) indicated that there is a need for capacity-building within countries with respect to making introduction and scale-up decisions across technologies and diseases in an integrated fashion, rather than only within disease areas. Ideally, these integrated decisions will be made in part by utilizing available epidemiologic and economic data appropriately; additional training by organizations like WHO or UNICEF could facilitate this.

Respondents noted that the start date for intensive engagement of country-level decision-makers is approximately at the end of Year -2. One respondent pointed out that this is because it is important to ensure that you have Phase 3 efficacy results prior to intensive engagement (Activity 1.2). In certain vaccine trials, interim Phase 3 data may be available before the end of Year -2 and form the basis for earlier engagement. Another respondent thought that engaging with decision-makers prior to this time may raise “false hopes” at the country-level about a new product (PHAR-D). It may also be difficult to sustain stakeholder attention over the longer duration of time (PHAR-D; PDP-D). For reformulations of existing products, this activity could possibly be compressed by a year, starting in Year -1. In other studies, PDPs have recommended country engagement as early as five years pre-licensure when a product is unusual and must be considered by multiple government departments (e.g., malaria program plus immunization program).²⁴ Engaging with key decision-makers in countries occurs at the same time as two parallel activities at the end of Year -2: **conducting regional workshops to share information and best practices (Activity 9.3)** and **conducting workshops to apply for financing in those countries that are GAVI-eligible (Activity 9.3V)**.

²³ See also Wells, W & Brooks, A. 2011. Adoption of new health products in low and middle income settings: how product development partnerships can support country decision making. *Health Research Policy and Systems*, 9(15). Available from: <http://www.health-policy-systems.com/content/9/1/15>.

²⁴ Ibid. p. 8.

Engaging with country-level decision-makers leads naturally into **planning for pilot/demonstration studies (Activity 9.4)** in those countries that express interest but request local evidence before full product roll out. The likelihood of countries requesting pilot/demonstration studies will depend on the product, disease area, and particular country. Pilot and demonstration studies are likely to be required by LMICs for novel technologies or for those products that may have political, cultural, or social sensitivities. In addition, certain countries may be more likely than others to require “local evidence” before deciding whether or not to select the product for use in the public sector. Planning for these studies occurs in Year -1 and lasts approximately until Year 1.

3.2 Downstream Activities on the Sample Gantt Charts, Year 0 to Year 5

Year 0 is the point in the timeline when marketing authorization is received for a drug or vaccine from a stringent or twinned regulatory filing. For the policymaking steps required subsequently, “decision making is driven by the country, not the PDP.”²⁵ The PDP’s role becomes less active and one of supporting, informing, and building capacity for existing country-level decision-making and implementation processes. The PDP’s work in this time period focuses on filing WHO prequalification and endemic country dossiers, supporting in-country partners in country policy review and pilot/demonstration projects, and supporting product adoption, rollout, and monitoring and evaluation.

Activity Group: Regulatory

Once SRA approval is obtained,²⁶ **WHO prequalification dossiers can be filed where relevant (Activity 5.5)**. For vaccines, WHO prequalification is critical to market access, as it allows for the procurement of the vaccine through UNICEF and is important for the vaccine to be considered for national immunization programs (PHAR-V). To begin the WHO prequalification process for vaccines, the product must be under the oversight of a regulatory authority deemed as “functional” by WHO.²⁷ In the sample Gantt charts in Appendix II, then, filing of WHO prequalification occurs just after SRA approval in Year 0.

Once WHO prequalification dossiers are filed, the time it takes to gain WHO prequalification for drugs varies from a few months to two years, depending on whether or not the product is undergoing the abridged process. For example, the time required for WHO prequalification for ASAQ Winthrop, a fixed-dose combination of artesunate and amodiaquine developed through a partnership between Sanofi-Aventis, DNDi, and MMV, was 20 months from the time of dossier

²⁵ Ibid, p. 8.

²⁶ For drugs, prequalification can proceed if the product has not been approved by an SRA. However, SRA approval is recognized by WHO which then uses an abridged process for prequalification. Ibid.

²⁷ Milstein, J & Brennan, M. 2010. PDP Regulatory Discussion Paper. October 2010. Available from: <http://pdpassess.org/downloads/projects/full-papers/PDP%20Regulatory%20Discussion%20Paper.pdf>.

submission.²⁸ For vaccines, the expected timing between the filing of WHO prequalification and approval is 1-1.5 years.

SRA approval in Year 0 also triggers the **filing of dossiers in endemic countries (Activity 5.7)**. These filings are generally not earlier, as regulatory authorities in many of the endemic countries either rely on a previous SRA approval or have a much faster process if the SRA approval is available. South Africa is one notable exception, and parallel filing may be advisable. Some PDPs are going to national regulatory authorities (NRAs) for first approval, but usually there is some extenuating circumstance for this, such as existing WHO prequalification, political support for the specific product, or technical transfer. In addition, most endemic countries other than South Africa require the certificate of pharmaceutical product (CPP) from the exporting country. Obtaining this may add approximately 6 months prior to starting Activity 5.7. Subsequent to NRA filing there is wide variability between endemic countries with respect to the time required to obtain product approval. One respondent describing the registration of a new formulation of an older drug stated that approval in the Democratic Republic of Congo was received in one day, whereas it took eight years for the product to be approved in South Africa (PHAR-D). One factor impacting the timing of approval was whether or not the company had people in country, on the ground, pushing the dossier forward for review.

Activity Group: Country Decision Support and Country Implementation

Supporting in-country partners in pilot/demonstration projects (Activity 10.1), where required, begins in Year 1 and lasts approximately two years (though this time will vary). It should begin following the approval of the regulatory dossiers in the pilot/demonstration country (Activity 5.7) because these studies cannot go ahead in most countries prior to registration.

The other country-level activity in this time period is **providing support for country policy review (Activity 10.2)**. This activity commences after SRA approval and WHO recommendation of the product. There are some examples where a national technical advisory group may consider a new intervention “in principle” before a preferred formulation is licensed in the country but, ultimately, the official adoption by the Ministry of Health will usually require prior registration by the NRA (Activity 5.7, see above). At best, the endemic country regulatory process and country adoption process may run concurrently (see Gantt charts in Appendix II), though in some countries the approximately 1 year required for the country decision process may start only once the regulatory process is finished. Thus, SRA approval, endemic country regulatory approval, and country decision-making may all have to occur sequentially (not shown in Gantt chart).

The duration required for country policy review varies greatly depending on the product and country policy processes. One study noted an average of one year for the basic decision-making

²⁸ Bompert, F., Kiechel, J.-R., Sebbag, R., Pecoul, B. Innovative public-private partnerships to maximize the delivery of anti-malarial medicines: Lessons learned from the ASAQ Winthrop experience. *Malaria Journal* 2011;10: 143.

process once the country had committed to consider a change.²⁹ The timeline of country policy review will be faster if products have significant demand in the country, address a problem with a sense of urgency, or have high-level champions. One PDP respondent noted that his organization believes that the process of the Ministry of Health reviewing and placing the drug (not the first to market in its class) into treatment guidelines as first line treatment will take three to five years (PDP-D). This is in contrast to the fast rate of policy review change to the anti-malarial Coartem® in many African countries following the perceived urgent need and demand for an artemisinin-combination therapy. Once a decision has been taken, revisions to national policies include changes in treatment guidelines, EPI program materials, Essential Medicines Lists, and formularies.

Activity Group: Ministry of Health Adoption and Roll Out

The third group of downstream activities involves the adoption and rollout of the product in the endemic country. The Gantt charts include two scenarios for product adoption. In reality, there may be an ongoing series of country adoption decisions taking people over many years, including “late adopting” countries, i.e. countries which prefer to wait for evidence from adoption and pilot projects in other countries before making a decision. These are not included on the Gantt charts because of their long and unpredictable timelines. The assumption is that partners will increasingly take over the work of interacting with countries on product adoption decisions over time.³⁰

The first scenario is in Year 1 and involves those **Ministries of Health that adopt the product based on WHO recommendation and existing product evidence (Milestone 10.3)**. Existing product evidence refers to results from pivotal Phase 3 and other studies and is provided to Ministries of Health in the standard evidence package mentioned earlier (Activity 6.3). The second product adoption scenario begins in Year 3 and involves those **Ministries of Health that adopt the product after reviewing evidence from pilot/demonstration projects and other country evidence (Milestone 10.5)**. PDP support to these pilot/demonstration projects (Activity 10.1) was mentioned above. There can be a significant gap between these two scenarios—one respondent mentioned that the gap in final adoption dates observed in his drug projects was four years (PHAR-D).

In the Gantt charts, the two adoption scenarios lead directly from their respective adoption decisions to roll out in Year 1 (Activity 10.4) or Year 3 (Activity 10.6), respectively. In reality, however, there is significant variation in timing as to how quickly products move from adoption to full roll out in the public sector. These variations are due to health systems factors (such as the efficiency of procurement, distribution, and delivery mechanisms), provider and end-user demand for the product, and global-level factors such as efficiency of donor financing and

²⁹ Wells, W.A., et al. Tuberculosis regimen change in high-burden countries. *Int. J Tuberc. Lung Dis.* 2010. 14:1538-1547.

³⁰ Wells, W & Brooks, A. 2011. Adoption of new health products in low and middle income settings: how product development partnerships can support country decision making. *Health Research Policy and Systems*, 9(15). Available from: <http://www.health-policy-systems.com/content/9/1/15>.

centralized procurement mechanisms in delivering the product to the country.³¹ Timing is also influenced by characteristics of the product—products that require certain storage conditions and new delivery systems, for example, may complicate and delay roll out in the public sector. Furthermore, both novel technologies that require training of providers and drugs that have end-user compliance issues will need informational materials to educate end-users on their appropriate use. Vaccines, on the other hand, usually work through existing procurement, distribution, and delivery systems and the timing of their roll out is more predictable.

Activity Group: Monitoring and Evaluation

The final group of downstream activities involves monitoring and evaluation. **Supporting the conduct of required post-licensure safety studies, routine pharmacovigilance, and safety reporting (Activity 11.1)** begins at Year 0. The start date of this activity is triggered by SRA or twinned marketing authorization (Activity 5.4; Year 0). The duration is estimated at three years but will vary, depending on study design and conditions in country. Safety issues where post-marketing studies or targeted pharmacovigilance are warranted will have been identified in Year -4 via ongoing dialogue with regulators (Activity 5.1; see above) and written into the plan for post-marketing surveillance (Activity 5.2; see above) developed in Year -3. One respondent noted that delays prior to this point of the timeline can occur if PDPs have not anticipated the post-marketing commitments on product safety required by regulators and developed these protocols in parallel with other activities usually conducted around the anticipated time of product approval (PHAR-V), since the product will not be approved without them. Optimally, this activity is conducted by the PDP's manufacturing partner, with PDPs providing support.³²

The second monitoring and evaluation activity involves **tracking product uptake and supporting the assessment of public health impact on disease incidence (Activity 11.2)**. This activity begins in Year 1, the first time point at which early adopting countries adopt the product based on WHO endorsement (Milestone 10.3) and runs until the PDP exits from the project (end point of the timeline). Planning for this activity may be part of the country decision making process and in some cases occurs prior to this point. While this activity is ideally conducted by the public sector of LMICs, several pharmaceutical and PDP respondents working on drug projects pointed out that a PDP's role in this activity may be a more active one if the necessary capacity does not exist in-country.

³¹ One year or longer delays have been documented due to failure to get sufficient funds into long-range budget plans, slow addition of a drug to a National Essential Medicines List, negotiating technology transfer between global and local manufacturers, procurement processes, and using up old drug stocks before a rollout. See Wells, W.A., et al. Tuberculosis regimen change in high-burden countries. *Int. J. Tuberc. Lung Dis.* 2010. 14:1538-1547.

³² Lalvani, P. & Milstein, J. 2011. Access to new health products in low income countries and the challenge of pharmacovigilance. May 2011. Available from: <http://pdpaccess.org/downloads/projects/full-papers/Pharmacovigilance%20Discussion%20Paper.pdf>.

4. Discussion and Conclusions

In Sections 3.1 and 3.2, we provided a detailed rationale of access activities for PDP consideration, the specific timing and linkages of these activities, and the conditions under which these timings may vary. These timelines reveal a progression from initial scoping of value proposition and strategy, through early engagement and collection of evidence, to an intensification of engagement and assembly of evidence into formal packages to support country and global decision making, and finally to more variable involvement in roll-out and surveillance activities.

It is important to note certain challenges with the study's methodology that could limit the generalizability of the findings. Many respondents had difficulties in seeing and reading the Gantt chart due to the sheer number of activities on the list. In many instances, the activities listed on the Gantt chart were too numerous to cover in detail in the amount of time designated for interviews (45 minutes to one hour). The interviewers sought to mitigate this by identifying two to four areas for more detailed consideration in each interview. Many respondents also found it difficult to commit to specific timings for specific projects and preferred to talk about timing issues in terms of generalities. In general, it was far easier for a respondent to talk about sequencing in relation to other activities, or to talk about general timing like "earlier" and "later."

Despite these caveats, the interviews provided numerous cross-cutting insights. One major finding of our research has been that it is far more difficult for respondents to pinpoint timing (and the conditions under which these timings vary) in downstream activities relative to the upstream access work. There are several reasons for this. First, decision-making processes and health systems can vary greatly between LMICs, making it difficult to generalize the time it takes to make decisions about products, to register them, to adopt them, and to roll them out. Given that most issues that arise unexpectedly will cause delays, our downstream timelines likely represent the most optimistic scenario. Second, most PDPs envisage a less active role in downstream activities, instead handing this work over to Ministries of Health and other partners in-country. Downstream access activities and their timing will differ depending on the PDP's particular involvement in downstream access work and the capabilities of their in-country partners. Finally, PDPs in general have less experience thus far with downstream activities since many of their products are still in the earlier phases of development. Some PDPs, however, have had experience downstream and this is an area that others can learn from to inform planning and decisions about their potential role. As more PDPs move their new products through licensure to country-level work, more detailed information about the timing of this work will be forthcoming. It will be important to categorize this work, however, based on the type of product, as downstream activities will vary significantly depending on the perceived importance and impact of the product of various stakeholders as well as the potential impact on health systems and budgets.

In the paper, we note that access timelines vary depending on the category of product. The findings indicate that timelines are generally shorter for interventions that are:

- Reformulations of existing technologies rather than entirely new (novel) inventions;
- Targeted against more (versus less) nationally or globally visible diseases;
- Easier to manufacture;
- For a vaccine, funded by GAVI rather than innovative or unpredictable financing;
- Responsive to an emergency outbreak.

We also mention in the paper a number of activities that respondents emphasized as taking longer than expected, and that therefore require PDPs to build sufficient time into their access timelines. These include the following manufacturing, financing, and in-country processes:

- Selecting, negotiating, and finalizing production agreements with manufacturers (Activity 4.3).
- Transferring manufacturing “know-how” (following Activity 4.3).
- Registration, adoption, and roll out in-country (Activities 5.7, 10.3-10.6)
- Discussing and finalizing innovative financing for upstream activities (Activity 7.2)

In addition to these activities that took longer than expected, respondents highlighted a range of issues that can cause delays in access timelines:

- Inaccurate demand forecasts can cause product supply to fall short (or exceed) actual product need and delay product roll out.
- Failure to fully anticipate post-marketing commitments on product safety required by regulators can delay SRA or twinned marketing authorization.
- Failure to negotiate early and periodically with regulators about follow-on manufacturing process improvements can lead to delays in regulatory approval and producing marketed product.
- Inability to obtain IP clearances from patent holders can lead to delays in finalizing production (and pricing) agreements with manufacturers.

To address these activities and broader issues that cause delays in access timelines, respondents pointed to key tactics that, properly implemented, can accelerate access timelines:

- Ensure that the data and statistical models used to generate strategic demand forecasts are accurate and up-to-date. In the Gantt charts, the activity to assess the burden of disease and unmet need (Activity 2.1) is done at Year -9.5 and the first high-level strategic demand forecast for global supply (Activity 4.1) is done at Year -7.5 and updated iteratively.
- Confer with regulators early (Activity 5.1; Year -9.5 on the Gantt charts) and continue this dialogue until dossier submission. This allows establishment of a relationship

between PDP staff and regulators and gives the PDP an understanding of the endpoints desired by regulators. It also helps anticipate post-marketing commitments on product safety, allows early negotiation about follow-on manufacturing process improvements, and educates regulators about diseases that they may not have worked on previously.

- Develop a robust regulatory strategy (Activity 2.4) at Year -9 that is modified iteratively based on assessments and strategies created for product rollout, financing, pricing, policy, and market.
- Use innovative financing mechanisms (Activity 7.2) as early as Year -7 to mitigate the risk to manufacturers in partnering with PDPs to produce marketed product.
- Conduct two sets of country studies at Year -4 (Defining key issues for and against introduction in particular countries (Activity 9.1) and studying target market's patients and healthcare providers (Activity 10.2D) to allow PDPs to present a more compelling case to Ministries of Health and other national stakeholders.
- Employ market research and conduct discussions with national and regional stakeholders throughout the process. Market research should consider the broader context of competing priorities and alternative interventions to fully understand the relative importance of new technologies. Stakeholder discussions should cover programmatic details that must be addressed early on, but are frequently not considered until the product is close to market and changes are not easily made (such as packaging volumes, doses/packaging, and storage and transportation concerns).

PDPs may experience human and financial resource constraints that make it difficult to operationalize these tactics for accelerating product access to end-users. They may therefore wish to call upon the additional expertise of KOLs involved in global expert groups (Activity 6.1). KOLs may provide necessary scientific expertise for meetings with regulators and advocate for financing, policy, and country adoption. Using the Gantt charts and this paper as a guide, PDPs can also seek funding to bring in the right people to assist with specific access activities at the right time in their access timelines.

Appendix I: List of Organizational Representatives Interviewed

Donors

- Jan Gheuens, Senior Program Officer, Bill and Melinda Gates Foundation
- Michael Kimerling, Senior Program Officer, Bill and Melinda Gates Foundation
- Saul Walker, Senior Policy Advisor, United Kingdom Department for International Development

Product Development Partnerships

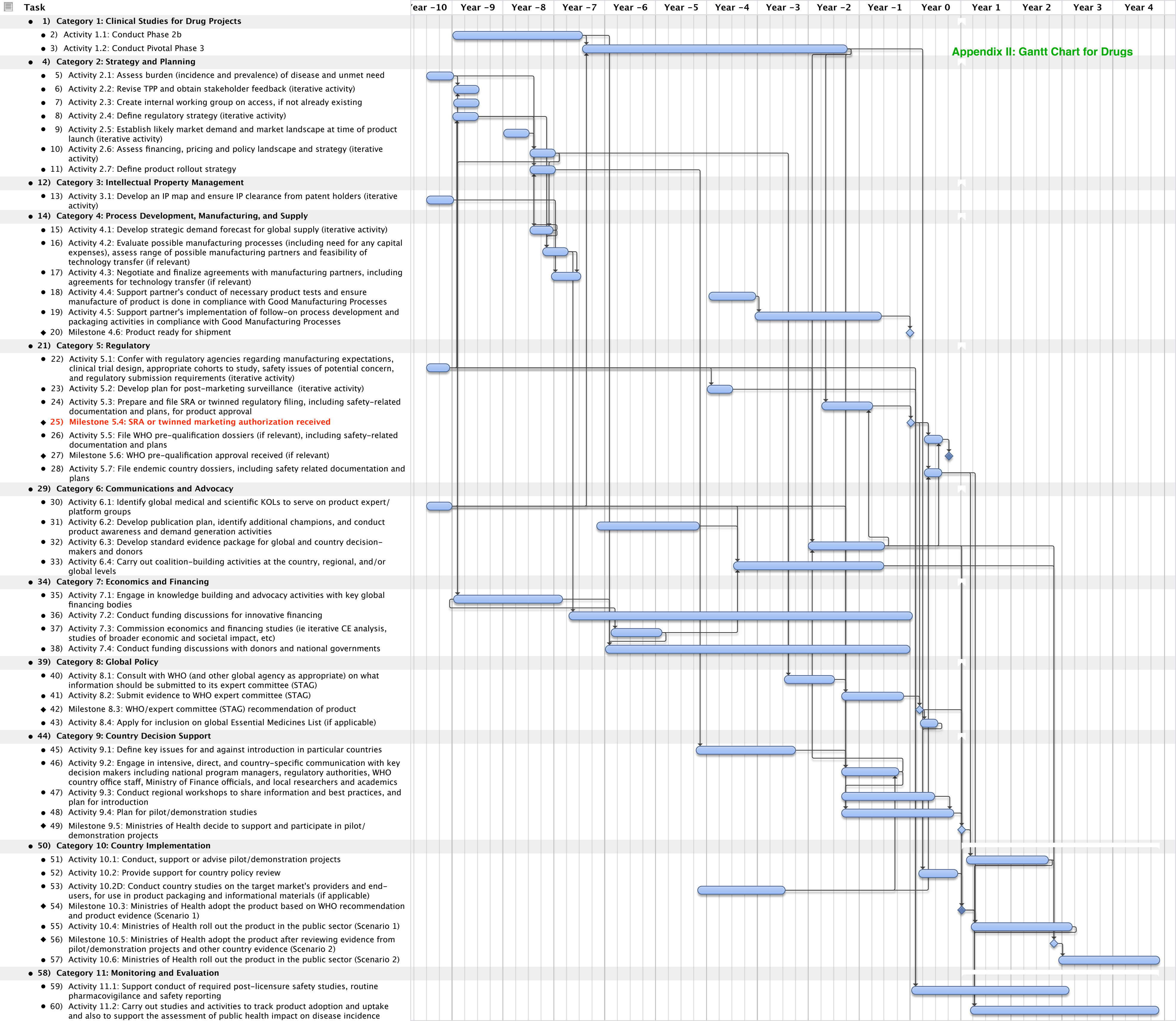
- Florence Camus-Bablon, Senior Access Advisor, Drugs for Neglected Diseases Initiative
- Julie Jacobson, Senior Program Officer, Bill and Melinda Gates Foundation (formerly Director of PATH's Japanese Encephalitis Project)
- George Jagoe, Executive Vice-President of Global Access, Medicines for Malaria Venture
- Lois Privor-Dumm, Director of Alliances and Information, International Vaccine Access Center

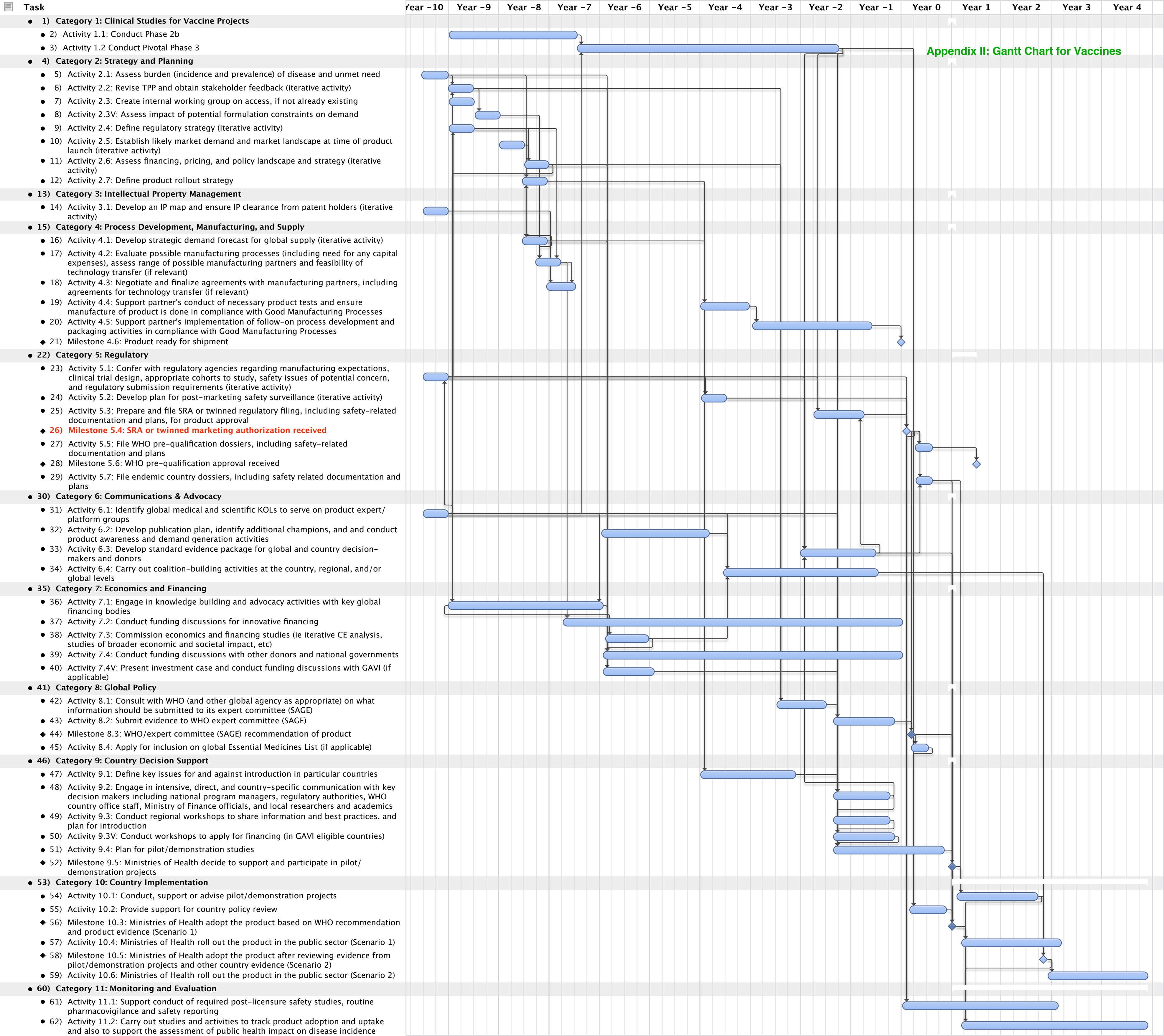
Pharmaceutical Companies

- Indranil Bagchi, Vice President of Market Access, Specialty Care Business Unit, Pfizer, Inc.
- François Bompard, Vice President, Deputy Head, Medical Director – Access to Medicines, Sanofi-Aventis
- Sandeep Duttgupta, Head of Market Access & Pricing, Emerging Markets Business Unit, Pfizer, Inc.
- Myriam Haxaire-Theeuwes, Senior Director Project Management, Tibotec
- Suresh Jadhav, Executive Director, Serum Institute of India
- Hans Rietveld, Director of Global Access and Marketing for the Novartis Malaria Initiatives, Novartis
- Allan Saul, CEO, Novartis Vaccines Institute for Global Health
- Representative of GlaxoSmithKline
- Representative of Merck

APPENDIX II:

GANTT CHARTS FOR DRUGS AND VACCINES, August 2011





Appendix III: Extensive List of Access Activities and Milestones for Consideration by PDPs

Table 1: Access Activities and Milestones for PDP Drug Projects

<i>Category 1: Clinical Studies</i>
<p><i>Activity 1.1:</i> Conduct Phase 2b</p> <p><i>Activity 1.2:</i> Conduct Pivotal Phase 3</p>
<i>Category 2: Strategy and Planning</i>
<p><i>Activity 2.1</i> Assess burden of disease, unmet need, and potential impact</p> <p><i>Activity 2.2:</i> Revise TPP</p> <p><i>Activity 2.3:</i> Conduct stakeholder analysis and/or market research to collect stakeholder feedback on TPP</p> <p><i>Activity 2.4:</i> Create internal working group on access, if not already existing</p> <p><i>Activity 2.5:</i> Identify information needs for all downstream activities (including country decision making, financing, etc) and integrate these information needs into R&D activities</p> <p><i>Activity 2.6:</i> Define regulatory strategy</p> <p><i>Activity 2.7:</i> Establish likely market demand and market landscape at time of product launch</p> <p><i>Activity 2.8:</i> Assess financing, pricing and policy landscape and strategy</p> <p><i>Activity 2.9:</i> Define advocacy strategy and key opinion leaders (KOL) strategy</p> <p><i>Activity 2.10:</i> Define product rollout strategy (priority countries, individual country challenges, partners)</p>
<i>Category 3: Intellectual Property Management</i>
<p><i>Activity 3.1:</i> Develop an IP map and ensure IP clearance from patent holders</p>
<i>Category 4: Process Development, Manufacturing, and Supply</i>
<p><i>Activity 4.1:</i> Develop strategic demand forecast for global supply</p> <p><i>Activity 4.2:</i> Evaluate possible manufacturing processes (including need for any capital expenses), assess range of possible manufacturing partners and feasibility of technology transfer (if relevant)</p> <p><i>Activity 4.3:</i> Select, negotiate, and finalize agreement with manufacturing partners for technology transfer (if relevant)</p> <p><i>Activity 4.4</i> Transfer technology to manufacturers (if relevant)</p> <p><i>Activity 4.5:</i> Support partner's conduct of necessary product tests and ensure manufacture of product is done in compliance with Good Manufacturing Processes</p> <p><i>Activity 4.6:</i> Support partner's implementation of follow-on process development and packaging activities in compliance with Good Manufacturing Processes</p>

<p><i>Activity 4.7:</i> Support partner's manufacture of product</p> <p><i>Milestone 4.8:</i> Product ready for shipment</p>
<i>Category 5: Regulatory</i>
<p><i>Activity 5.1:</i> Confer with regulatory agencies regarding manufacturing expectations, clinical trial design, appropriate cohorts to study, safety issues of potential concern, and regulatory submission requirements (iterative activity)</p> <p><i>Activity 5.2:</i> Develop plan for post-marketing surveillance</p> <p><i>Activity 5.3:</i> Prepare SRA or twinned regulatory filing for product approval</p> <p><i>Activity 5.4:</i> File SRA or twinned regulatory dossier for product approval</p> <p><i>Milestone 5.5:</i> SRA or twinned marketing authorization received</p> <p><i>Activity 5.6:</i> Prepare WHO prequalification dossier for product approval if appropriate/feasible</p> <p><i>Activity 5.7:</i> File WHO prequalification dossier for product approval</p> <p><i>Milestone 5.8:</i> WHO prequalification product approval received</p> <p><i>Activity 5.9:</i> Prepare endemic country dossiers for registration</p> <p><i>Activity 5.10:</i> File country-specific dossiers for registration</p> <p><i>Milestone 5.11:</i> Marketing authorization received from endemic country regulatory agencies</p>
<i>Category 6: Communications and Advocacy</i>
<p><i>Activity 6.1:</i> Identify global medical and scientific KOLs to serve on product expert/platform groups</p> <p><i>Activity 6.2:</i> Develop publication plan, identify additional champions, and conduct product awareness and demand generation activities</p> <p><i>Activity 6.3:</i> Develop standard evidence package for global and country decision-makers and donors</p> <p><i>Activity 6.4:</i> Work with advocates locally, regionally and internationally, and develop advocacy capacity</p> <p><i>Activity 6.5:</i> Carry out coalition-building activities at the country, regional, and/or global levels</p>
<i>Category 7: Economics and Financing</i>
<p><i>Activity 7.1:</i> Engage in policy discussions, knowledge building and advocacy activities with key global financing bodies</p> <p><i>Activity 7.2:</i> Identify potential sources of innovative financing and conduct funding discussion</p> <p><i>Activity 7.3:</i> Commission preliminary cost-effectiveness studies (assessing a range of cost and effectiveness scenarios)</p> <p><i>Activity 7.4:</i> Commission willingness-to-pay studies, as needed</p> <p><i>Activity 7.5:</i> Support studies by external experts on broader economic and societal impacts of the product</p> <p><i>Activity 7.6:</i> Refine cost-effectiveness estimates, based on Phase 3 data</p> <p><i>Activity 7.7:</i> Conduct funding discussions with donors and national governments</p>
<i>Category 8: Global Policy</i>

<p><i>Activity 8.1:</i> Consult with WHO (and other global agency as appropriate) on what information should be submitted to its expert committee (STAG)</p> <p><i>Activity 8.2:</i> Submit evidence to WHO/expert committee for endorsement of product</p> <p><i>Milestone 8.3:</i> WHO/expert committee recommendation of product</p> <p><i>Activity 8.4:</i> Support WHO in updating global policies and guidelines, as appropriate</p> <p><i>Activity 8.5:</i> Apply for inclusion on global Essential Medicines List (if applicable)</p>
<i>Category 9: Country Decision Support</i>
<p><i>Activity 9.1:</i> Define key issues for and against introduction in particular countries</p> <p><i>Activity 9.2:</i> Identify key decision makers at the country level and conduct stakeholder analysis</p> <p><i>Activity 9.3:</i> Assess local regulatory issues regarding product registration, Essential Medicines List and guideline changes</p> <p><i>Activity 9.4:</i> Engage in intensive, direct, and country-specific communication with key decision makers including national program managers, regulatory authorities, WHO country office staff, Ministry of Finance officials, and local researchers and academics</p> <p><i>Activity 9.5:</i> Disseminate a country-specific evidence package for decision making</p> <p><i>Activity 9.6:</i> Support, in individual countries or regions, the development of a country framework for reaching evidence-based decisions on introduction</p> <p><i>Activity 9.7:</i> Conduct regional workshops to share information and best practices, and plan for introduction</p> <p><i>Activity 9.8:</i> Plan pilot/demonstration studies (evaluate and engage possible sites, determine scope, objectives and implementing agencies, apply for internal ethics clearance)</p> <p><i>Milestone 9.9:</i> Ministries of Health decide to support and participate in pilot/demonstration projects</p>
<i>Category 10: Country Implementation</i>
<p><i>Activity 10.1:</i> Conduct, support or advise pilot/demonstration projects Provide support for country policy review</p> <p><i>Activity 10.2:</i> Partner with relevant Ministry of Health units with introduction preparation (including procurement, training, IEC/BCC materials, systems upgrades, M&E, or other operational issues)</p> <p><i>Activity 10.3:</i> Conduct country studies on the target market's providers and end-users, for use in product packaging and informational materials (if applicable)</p> <p><i>Milestone 10.4:</i> Ministries of Health adopt the product based on WHO recommendation and product evidence (Scenario 1)</p> <p><i>Activity 10.5:</i> Ministries of Health roll out product in public sector (Scenario 1)</p> <p><i>Milestone 10.6:</i> Ministries of Health adopt the product after reviewing evidence from pilot/demonstration projects and other country evidence (Scenario 2)</p> <p><i>Activity 10.7:</i> Ministries of Health roll out product in public sector (Scenario 2)</p>
<i>Category 11: Monitoring and Evaluation</i>
<i>Activity 11.1:</i> Support conduct of required post-licensure safety studies, routine

<p>pharmacovigilance and safety reporting</p> <p><i>Activity 11.2:</i> Carry out studies and activities to track product adoption and uptake and also to support the assessment of public health impact on disease incidence</p>
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Table 2: Access Activities and Milestones for PDP Vaccine Projects

<i>Category 1: Clinical Studies</i>
<p><i>Activity 1.1:</i> Conduct Phase 2b</p> <p><i>Activity 1.2:</i> Conduct Pivotal Phase 3</p>
<i>Category 2: Strategy and Planning</i>
<p><i>Activity 2.1</i> Assess burden of disease, unmet need, and potential impact</p> <p><i>Activity 2.2:</i> Revise TPP</p> <p><i>Activity 2.3:</i> Conduct stakeholder analysis and/or market research to collect stakeholder feedback on TPP</p> <p><i>Activity 2.4:</i> Create internal working group on access, if not already existing</p> <p><i>Activity 2.5:</i> Identify information needs for all downstream activities (including country decision making, financing, etc) and integrate these information needs into R&D activities</p> <p><i>Activity 2.6:</i> Assess impact of potential formulation constraints on demand</p> <p><i>Activity 2.7:</i> Define regulatory strategy</p> <p><i>Activity 2.8:</i> Establish likely market demand and market landscape at time of product launch</p> <p><i>Activity 2.9:</i> Assess financing, pricing and policy landscape and strategy</p> <p><i>Activity 2.10:</i> Define advocacy strategy and key opinion leaders (KOL) strategy</p> <p><i>Activity 2.11:</i> Define product rollout strategy (priority countries, individual country challenges, partners)</p>
<i>Category 3: Intellectual Property Management</i>
<p><i>Activity 3.1:</i> Develop an IP map and ensure IP clearance from patent holders</p>
<i>Category 4: Process Development, Manufacturing, and Supply</i>
<p><i>Activity 4.1:</i> Develop strategic demand forecast for global supply</p> <p><i>Activity 4.2:</i> Evaluate possible manufacturing processes (including need for any capital expenses), assess range of possible manufacturing partners and feasibility of technology transfer (if relevant)</p> <p><i>Activity 4.3:</i> Select, negotiate, and finalize agreement with manufacturing partners for technology transfer (if relevant)</p> <p><i>Activity 4.4</i> Transfer technology to manufacturers (if relevant)</p> <p><i>Activity 4.5:</i> Support partner's conduct of necessary product tests and ensure manufacture of product is done in compliance with Good Manufacturing Processes</p> <p><i>Activity 4.6:</i> Support partner's implementation of follow-on process development and packaging activities in compliance with Good Manufacturing Processes</p>

<p><i>Activity 4.7:</i> Support partner's manufacture of product</p> <p><i>Milestone 4.8:</i> Product ready for shipment</p>
<p><i>Category 5: Regulatory</i></p>
<p><i>Activity 5.1:</i> Confer with regulatory agencies regarding manufacturing expectations, clinical trial design, appropriate cohorts to study, safety issues of potential concern, and regulatory submission requirements (iterative activity)</p> <p><i>Activity 5.2:</i> Develop plan for post-marketing surveillance</p> <p><i>Activity 5.3:</i> Prepare SRA or twinned regulatory filing for product approval</p> <p><i>Activity 5.4:</i> File SRA or twinned regulatory dossier for product approval</p> <p><i>Milestone 5.5:</i> SRA or twinned marketing authorization received</p> <p><i>Activity 5.6:</i> Prepare WHO prequalification dossier for product approval if appropriate/feasible</p> <p><i>Activity 5.7:</i> File WHO prequalification dossier for product approval</p> <p><i>Milestone 5.8:</i> WHO prequalification product approval received</p> <p><i>Activity 5.9:</i> Prepare endemic country dossiers for registration</p> <p><i>Activity 5.10:</i> File country-specific dossiers for registration</p> <p><i>Milestone 5.11:</i> Marketing authorization received from endemic country regulatory agencies</p>
<p><i>Category 6: Communications and Advocacy</i></p>
<p><i>Activity 6.1:</i> Identify global medical and scientific KOLs to serve on product expert/platform groups</p> <p><i>Activity 6.2:</i> Develop publication plan, identify additional champions, and conduct product awareness and demand generation activities</p> <p><i>Activity 6.3:</i> Develop standard evidence package for global and country decision-makers and donors</p> <p><i>Activity 6.4:</i> Work with advocates locally, regionally and internationally, and develop advocacy capacity</p> <p><i>Activity 6.5:</i> Carry out coalition-building activities at the country, regional, and/or global levels</p>
<p><i>Category 7: Economics and Financing</i></p>
<p><i>Activity 7.1:</i> Engage in policy discussions, knowledge building and advocacy activities with key global financing bodies</p> <p><i>Activity 7.2:</i> Identify potential sources of innovative financing and conduct funding discussion</p> <p><i>Activity 7.3:</i> Commission preliminary cost-effectiveness studies (assessing a range of cost and effectiveness scenarios)</p> <p><i>Activity 7.4:</i> Commission willingness-to-pay studies, as needed</p> <p><i>Activity 7.5:</i> Support studies by external experts on broader economic and societal impacts of the product</p> <p><i>Activity 7.6:</i> Refine cost-effectiveness estimates, based on Phase 3 data</p> <p><i>Activity 7.7:</i> Conduct funding discussions with donors and national governments</p> <p><i>Activity 7.9:</i> Present investment case and conduct funding discussions with GAVI (if</p>

applicable)
<i>Category 8: Global Policy</i>
<p><i>Activity 8.1:</i> Consult with WHO (and other global agency as appropriate) on what information should be submitted to its expert committee (SAGE)</p> <p><i>Activity 8.2:</i> Submit evidence to WHO/expert committee for endorsement of product</p> <p><i>Milestone 8.3:</i> WHO/expert committee recommendation of product</p> <p><i>Activity 8.4:</i> Support WHO in updating global policies and guidelines, as appropriate</p> <p><i>Activity 8.5:</i> Apply for inclusion on global Essential Medicines List (if applicable)</p>
<i>Category 9: Country Decision Support</i>
<p><i>Activity 9.1:</i> Define key issues for and against introduction in particular countries</p> <p><i>Activity 9.2:</i> Identify key decision makers at the country level and conduct stakeholder analysis</p> <p><i>Activity 9.3:</i> Assess local regulatory issues regarding product registration, Essential Medicines List and guideline changes</p> <p><i>Activity 9.4:</i> Engage in intensive, direct, and country-specific communication with key decision makers including national program managers, regulatory authorities, WHO country office staff, Ministry of Finance officials, and local researchers and academics</p> <p><i>Activity 9.5:</i> Disseminate a country-specific evidence package for decision making</p> <p><i>Activity 9.6:</i> Support, in individual countries or regions, the development of a country framework for reaching evidence-based decisions on introduction</p> <p><i>Activity 9.7:</i> Conduct regional workshops to share information and best practices, and plan for introduction</p> <p><i>Activity 9.8:</i> Conduct workshops to apply for financing (in GAVI eligible countries)</p> <p><i>Activity 9.9:</i> Plan pilot/demonstration studies (evaluate and engage possible sites, determine scope, objectives and implementing agencies, apply for internal ethics clearance)</p> <p><i>Milestone 9.10:</i> Ministries of Health decide to support and participate in pilot/demonstration projects</p>
<i>Category 10: Country Implementation</i>
<p><i>Activity 10.1:</i> Conduct, support or advise pilot/demonstration projects Provide support for country policy review</p> <p><i>Activity 10.2:</i> Partner with relevant Ministry of Health units with introduction preparation (including procurement, training, IEC/BCC materials, systems upgrades, M&E, or other operational issues)</p> <p><i>Milestone 10.3:</i> Ministries of Health adopt the product based on WHO recommendation and product evidence (Scenario 1)</p> <p><i>Activity 10.4:</i> Ministries of Health roll out product in public sector (Scenario 1)</p> <p><i>Milestone 10.5:</i> Ministries of Health adopt the product after reviewing evidence from pilot/demonstration projects and other country evidence (Scenario 2)</p> <p><i>Activity 10.6:</i> Ministries of Health roll out product in public sector (Scenario 2)</p>

<i>Category 11: Monitoring and Evaluation</i>
<i>Activity 11.1:</i> Support conduct of required post-licensure safety studies, routine pharmacovigilance and safety reporting
<i>Activity 11.2:</i> Carry out studies and activities to track product adoption and uptake and also to support the assessment of public health impact on disease incidence

Appendix IV: Authors' Biographies

Laura Frost

Laura Frost is a partner and co-founder of Global Health Insights. She has worked with many different global health organizations on a range of issues such as access to health technologies, public-private partnerships, health financing, and agenda setting. She has completed a book (with Michael R. Reich) called *Access: How Do Good Technologies Get to Poor People in Poor Countries?* (Cambridge, MA: Harvard Center for Population and Development Studies, 2008). Laura is currently an Adjunct Lecturer in Population and Family Health at Columbia University's Mailman School of Public Health. Previously, she was Lecturer in Public & International Affairs at Princeton University's Woodrow Wilson School where she taught undergraduate and graduate courses on international health policy and access to medicines for HIV/AIDS and neglected diseases. Laura has also taught research methods and global health policy to medical students at University College Cork in Ireland, where she carried out a three-year qualitative and quantitative research project on perceptions, practices, and promotion of breastfeeding in Ireland. Laura has lived and worked in east, central, and southern Africa and worked with non-governmental organizations on community-based health programs in relief and development contexts. Laura earned a MALD (Fletcher School of Law and Diplomacy, Tufts University), MPH, and Doctor of Science in International Health (Harvard School of Public Health). She is presently based in Bujumbura, Burundi.

Sybil Eng

Sybil Eng is a freelance epidemiologist and consultant for Global Health Insights, where she lends her expertise to interview-based field studies. Prior to this, she was a Senior Director and the Specialty Care Business Unit Head in Pfizer's Epidemiology group, where she managed a team of eight epidemiologists. She led and oversaw the development of risk management strategies, varying from postapproval observational study commitments to routine and targeted pharmacovigilance plans to extensions of long-term clinical trials, for the company's medicines across a range of therapeutic areas, including anti-infectives (HIV/AIDS, antifungals, and antibiotics), neuroscience (antipsychotics, antidepressants), and respiratory disease. She has worked with cross-functional clinical development teams on safety issues for drug candidates spanning the development lifecycle from new molecular entities to registered medicines, at times representing the company at key meetings with regulatory agencies. Notable achievements include scientific and operational oversight of a study of HIV co-receptor tropism conducted among HIV-infected patients in Uganda and South Africa as well as an 18,000-patient large simple trial of novel design conducted among patients with schizophrenia enrolled from 18 countries in North America, Europe, and Asia. Sybil earned Doctor of Philosophy and Master of Public Health degrees from Columbia University.

Beth Anne Pratt

Beth Anne Pratt is a partner and co-founder of Global Health Insights. Presently based in Lusaka , Zambia, she focuses primarily on issues involving health systems and national/sub-national access to technologies, services, and financing in developing countries. In 2003, she received her PhD in social anthropology from Boston University. Her research focused on childhood and social, economic, and political change among Kisongo Maasai in northern Tanzania. Living and working for two years in a rural African community shaped her insight into the ways that service provision is so often misunderstood within and between cultures. Since then, she has had wide-ranging, cross-sectoral experience working on livelihoods issues in a number of African countries, including Tanzania, Uganda and Kenya. She has also worked on volunteerism and corporate social responsibility projects in Cairo. Beth brings an interdisciplinary perspective and a strong capacity for qualitative research, synthesis, contextualization, and thick description.