

Road Map for Scaling Up ACTs: 2004 and Beyond

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About RPM Plus

RPM Plus works in more than 20 developing and transitional countries to provide technical assistance to strengthen drug and health commodity management systems. The program offers technical guidance and assists in strategy development and program implementation in improving the availability of health commodities—pharmaceuticals, vaccines, supplies, and basic medical equipment—of assured quality for maternal and child health, HIV/AIDS, infectious diseases, and family planning, as well as in promoting the appropriate use of health commodities in the public and private sectors.

About the RBM Partnership

To provide a coordinated global approach to fighting malaria, the RBM Partnership was launched in 1998 by the World Health Organization (WHO), the United Nations Children’s Fund (UNICEF), the United Nations Development Programme (UNDP), and the World Bank. The RBM Partnership’s goal is to halve the global malaria burden by 2010.

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Acronyms

ACT	artemisinin-based combination therapy
API	active pharmaceutical ingredient
BCC	behavior change communication
EDM	Department of Essential Drugs and Medicines Policy [WHO]
EOI	Expression of Interest
GMP	Good Manufacturing Practices
HIPC	heavily indebted poor country
HMIS	health management information system
ICH	International Conference on Harmonisation
IEC	information, education, and communication
IMCI	Integrated Management for Childhood Illness
ITN	insecticide-treated net
M&E	monitoring and evaluation
MMSS	Malaria Medicines and Supplies Service
MMV	Medicines for Malaria Venture
NGO	nongovernmental organization
QA	quality assurance
QSM	Quality Assurance and Safety of Medicines [WHO]
RBM	Roll Back Malaria
RDT	rapid diagnostic test
SWAP	sector-wide approach
TDR	Special Programme for Research and Training in Tropical Diseases
UN	United Nations
UNICEF	United Nations Children's Fund
USD	U.S. dollar
WHO	World Health Organization

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Executive Summary

This road map is intended to facilitate collaboration within the Roll Back Malaria (RBM) Partnership to meet the short-term needs of those countries that have adopted or that will adopt artemisinin-based combination therapies (ACTs) in 2004, and to outline critical steps, bottlenecks, and milestones in the production, prequalification, registration, procurement, and sourcing of ACTs in the medium term (2005–2006). This road map focuses on access to ACTs within the public health care sector in sub-Saharan Africa because the initial implementation of ACTs with active government participation at national levels has been within this sector. Nevertheless, ACTs are reaching end users through a variety of distribution systems, including the private nonprofit sector and informal private providers, so efforts to regulate, ensure efficient distribution, and promote the correct use of ACTs in these sectors are also needed.

Switching from the monotherapies that have been used as standard treatment for malaria for many years to the recommended combination treatments is a complex undertaking, requiring a set of activities within each country to assemble evidence of drug resistance; assess new treatment options; and make the critical decision to change, find financing, and then implement the new treatments. Many stakeholders are involved, ranging from Ministries of Health to providers in the private sector to the end users or consumers of ACTs. In parallel with the steps that countries are taking to deploy ACTs, production of both the active pharmaceutical ingredient (API) and the finished product must be scaled up because current world production appears to fall short of projected needs.

At the global level, multilateral and bilateral institutions, agencies of the United Nations (UN), the pharmaceutical industry, nongovernmental organizations (NGOs), and research institutions are also confronted by the challenges involved in ensuring that ACTs are accessible to and appropriately used by those who need them.

Although each country presents a unique set of challenges and opportunities, the actions that are required to improve access to ACTs can be outlined in a way that will permit stakeholders to identify how each can contribute. Therefore, this road map identifies the critical steps needed in a two-pronged strategy that addresses both short-term and medium-term needs. These steps can be categorized as: (i) actions that need to be taken at country level for deployment and implementation; (ii) production; (iii) procurement; (iv) distribution; (v) prequalification; and (vi) registration and regulation. For each of these categories, critical steps, milestones, bottlenecks, and the potential contribution of the RBM Partnership are suggested in an effort to develop a framework that will help stakeholders coordinate their activities. The text of this document is supplemented by diagrams at the end of each section that summarize each issue. Annex 1 provides a diagram summarizing the entire road map.

The conclusion highlights suggested next steps. Principal among these is the recommendation that the RBM Secretariat take the lead in defining the roles of the different RBM Partners in making the road map and the Malaria Medicines and Supplies Service (MMSS) operational.

Last, it should be recognized that activities are already under way for improving access to ACTs, with many RBM Partners already working hard in the field and at the global level. The facts upon which this road map is based are current as of early April 2004. As activities for scaling up ACT access continue and the full range of actions needed to improve access to ACTs is implemented, this document could be useful as a tool for monitoring progress.

Background

A strong consensus exists on ACT as the first choice for combination therapy to treat malaria when drug resistance to monotherapy is experienced, and the use of combination therapy has been recommended by the World Health Organization (WHO) since 2001 (WHO 2001), with a position statement on effective case management issued in 2004 by the RBM Board (RBM 2004a). In sub-Saharan Africa, ACT adoption is gathering increasing momentum. The magnitude and complexity of the challenges that these shifts in treatment policy will pose are highlighted by comparing recent demand forecasts for sub-Saharan Africa and the world made by WHO (WHO/UNICEF 2004) with current world capacity for ACT production (Table 1).

YEAR	DEMAND FORECAST		PRODUCTION CAPACITY
	Sub-Saharan Africa	World	World
2004	18 000 000	31 000 000	50 000 000
2005–2006	92 000 000	153 000 000	50 000 000 – 100 000 000

Table 1. ACT Needs Forecast

The challenges of increasing access to and use of ACTs span many domains on both the demand side and the supply side. A preliminary estimate of the financing needs suggests that USD 30–60 million will be needed to procure ACTs in 2004, and between USD 130 and USD 200 million will be needed annually for 2005–2006. These needs will increase as more countries implement the shift to ACTs. Besides the financing challenge, procurement systems have to be strengthened, distribution strategies have to be developed, and monitoring and evaluation (M&E) systems need to be put in place, to name just a few of the additional areas that will require RBM Partnership support. On the supply side, ACTs pose unique challenges—first, because they include artemisinin, an herbal component that requires a long planting cycle, and second, because although the absence of a patent on artemisinin and its derivatives has permitted many manufacturers of generic formulations to enter the market, in many cases these manufacturers have not carried out the extensive safety and efficacy studies that are typically done for branded drugs produced by innovator companies.

The RBM Partnership will establish a new “drug facility” mechanism, the Malaria Medicines and Supplies Service, which will be mandated to support the efforts of malaria-endemic countries in accessing quality and affordable antimalarial medicines and other supplies, including rapid diagnostic tests (RDTs) and insecticide-treated nets (ITNs). The MMSS will work with partners to facilitate and coordinate activities across the value chain, including financing and supply chain management, with direct impact in five areas: product quality assurance (QA), standardization/simplification, cost/affordability, reliability of supply, and speed in delivery of supplies.

The RBM Partners recognize that during the start-up phase of MMSS, technical and program actions will be required to ensure timely and effective support to meet the immediate needs for 2004.

Meeting Immediate Needs for ACT Access: 2004

As of April 2004, 14 countries had adopted ACTs as first- or second-line therapy (WHO-RBM 2004), and a few sub-Saharan countries have already accumulated experience with their implementation. The RBM Partnership has also identified a set of focus countries that are considered ready to go to scale in attaining targets set by the 2000 Abuja Declaration. These experiences, some of which have been shared at meetings sponsored by WHO and the RBM Partnership, include not only financing issues but also a range of bottlenecks that have been encountered on the community level (e.g., lack of awareness), during the procurement process (e.g., lack of information on suppliers of quality ACTs), and during distribution (e.g., lack of adequate packaging materials for co-packaging artesunate with amodiaquine).

The complexity and breadth of these issues reinforce the need to tap the deep levels of technical expertise available within the RBM Partnership, as well as actual financial resources, to address both the needs for 2004 and the longer-term needs for 2005 and beyond.

To meet the financial and procurement needs for 2004, the RBM Partnership will identify resources that could be made available from existing funding mechanisms. These include funds that have been approved, that are under grant agreement, or that have been disbursed through the first three rounds of funding by the Global Fund to Fight AIDS, Tuberculosis and Malaria. The Global Fund has agreed to allow the reallocation of approved and disbursed funds for the purchase of ACTs, including those funds previously earmarked for services as well as those earmarked for medicine and supply purchases, provided that the public health objectives outlined in the original approved proposal are met. Other potential sources of funding at country level include sources within the health sector, such as sector-wide approach (SWAP) financing, and outside the health sector, such as heavily indebted poor country (HIPC) funds and the general government budget (World Bank 2003).

For procurement, the RBM Partnership recognizes that the number of WHO/United Nations Children's Fund (UNICEF) prequalified suppliers of ACTs as of early 2004 is insufficient and is seeking to identify suppliers of acceptable-quality ACTs on a provisional basis while the formal prequalification process continues.

Acting on available information, the RBM Partnership has already started undertaking the following steps at the global level:

- Mapping out resources that could be made available to purchase ACTs from funds already approved or disbursed by the Global Fund in Rounds 1–3
- Working with countries to ensure that the requests made for ACTs in future Global Fund proposals correspond to both implementation schedules and available funding
- Identifying additional suppliers of acceptable-quality ACTs
- Continuing the prequalification process

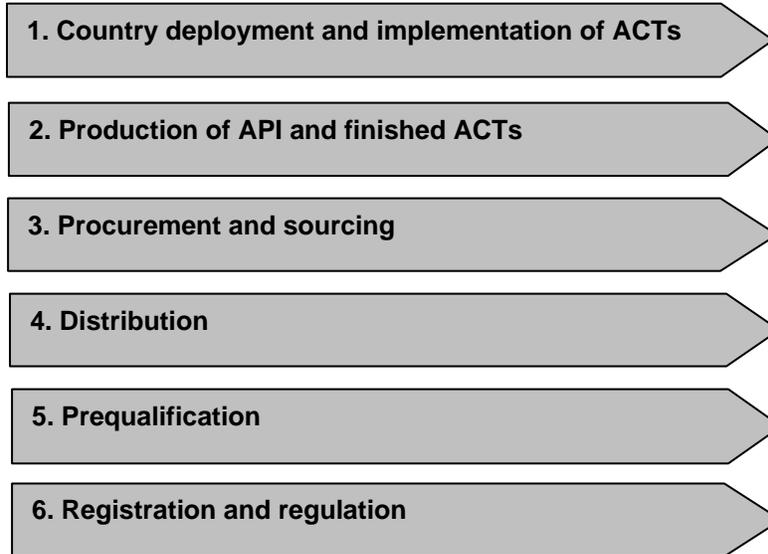
- Compiling a list of sources and prices that includes information on ACT suppliers
- Making MMSS operational

The preceding outline of activities represents those that can be carried out on a global basis; they should be complemented by a focused set of activities at country level to generate detailed forecasts of ACT needs for 2004, including the following:

- Gathering information on implementation and rollout plans, with associated timelines, in those countries that will be adopting ACTs in 2004
- Matching the resulting requirements for ACTs against available funding through the mechanisms highlighted above

These country-level activities will permit a coordinated effort in planning by the RBM Partnership on how to fill in the gaps.

Medium-Term and Longer-Term Phases: 2005–2006 and Beyond



Current forecasts for worldwide demand of ACTs indicate that at least a threefold increase over the present worldwide production capacity will be needed to ensure that high-quality ACTs are available to satisfy the increased demand by 2005 alone. Worldwide needs for ACTs will continue to grow over the next several years, necessitating even higher production capacity. To reach the goal of providing ACTs for all those who need them, substantial increases in both the production of the API and the production of the finished ACTs will be required.

This part of the road map builds on a consensus approach developed by the RBM Partnership (RBM 2004a; 2004b) and outlines the critical steps, bottlenecks, and milestones in six relevant areas as well as activities that the RBM Partnership could undertake in each of these areas. Each of the six sections is followed by a graphic depiction for easy reference. Although these six areas are described sequentially in this document, it is important to keep in mind that success in achieving the shared goals of ACT access will require that activities in these areas advance in parallel.

1. Country Deployment and Implementation of ACTs

1.1. Critical Steps

Making the decision to change drug policy and adopt a new treatment with which a national health care system may have little experience requires considerable preparation and work at the country level. A situation analysis is first required, including an assessment of the performance of existing treatments and an assessment of options. Available resources need to be considered, both financial and technical. It is generally desirable to have clinical study data available to guide

decision making, both for currently existing treatments and for proposed new treatments, but this information is not always available. Many stakeholders are involved, including clients or consumers of health services, government ministries, and NGOs and donor partners who are present within the country. Experience in countries shows that consensus building among these groups is often needed before making the actual decision to change drug treatment policy.

After the situation analysis has been completed, the decision to change drug policy sets in motion several tasks that can be performed in parallel. Typically, working groups or committees will be established to tackle several areas, including the following:

- **Drug supply and management issues:** The relatively short shelf life of ACTs and the need to supply some of them in co-packaged form distinguish ACTs from most drugs that flow through national health systems. Other considerations will include the needs for quality assurance and quality control, as well as the need to prevent ACTs that are bought for the public sector from being diverted into the private health care sector. Plans need to be developed in order to withdraw and safely dispose of existing stocks of drugs that will no longer be used.
- **Development of national treatment guidelines:** These guidelines have to be country-specific and should reflect the eventual availability of the different forms of ACTs (i.e., co-packaged in blister packs or co-formulated). The role of diagnostic aids, such as RDTs, needs to be defined, taking into account local or regional malaria prevalence. Training programs and materials on rational drug use and drug management need to be organized for health care providers, including community health workers, nurses, doctors, and pharmacists. Integrated Management of Childhood Illness (IMCI) materials need to be updated.
- **Drug registration:** The ACTs that are chosen for treatment options must be authorized for sale on the market, which is generally done through the process of registration. Drug regulatory authorities must take steps to prevent substandard and counterfeit products from entering the country and to reinforce pharmacovigilance activities.
- **Demand forecast:** Several different methods can be used to compile a needs forecast, including consumption-based methods and morbidity-based methods. This activity is often a challenge in situations where drug consumption data are lacking or health management information systems (HMISs) are not fully functioning.
- **Financing/resource mobilization:** Financial resources that can be used for national-level procurements will include national government budgets; multilateral and bilateral institutions, such as the World Bank and the Global Fund; NGOs; and foundations. At the user level, out-of-pocket payments and cost-recovery systems need to be decided on.
- **Distribution plans:** The few sub-Saharan African countries that have adopted ACTs have initially focused on making ACTs available in the public sector, but strategies for distribution through the private sector, where an estimated 60 percent or more of the population receives oral treatments for malaria (Kindermans 2004), will have to be

developed. Reaching the private sector is crucial not only for ensuring access to ACTs, but also for avoiding the use of monotherapies that may be sold through the private sector and which could become problematic if regulation and distribution through the private sector is not planned for. In addition, the role and use of RDTs have to be defined. Distribution plans for both the public and private sectors have to include the use of subsidy mechanisms; otherwise, ACTs will be unaffordable to large segments of the population.

- **Information, education, and communication (IEC) and behavior change communication (BCC):** Uptake and acceptance of ACTs by the general population and throughout the health care sector will require planning for IEC and BCC campaigns.
- **Monitoring and evaluation:** Traditionally this set of activities has been given less of a priority than others. However, stakeholders are increasingly demanding evidence of results. Therefore, planning for M&E of ACT deployment and implementation should be integrated early so that pertinent data will be available in a timely fashion to guide country malaria programs, governments, and external stakeholders.

The next critical step for countries to take is procurement of ACTs. This area is treated in more detail in Section 3.

As ACT supplies arrive in the country, rollout and distribution to households, health facilities, the private health care sector, and the community have to take place. Strong supply chain management systems are needed. The last critical step is to ensure effective case management. Effective case management will depend on all the elements outlined above coming together so that the right drug reaches the right patient, in the right dose, at the right time and so that the treatment is affordable to the person who needs it.

1.2. Milestones

The following list represents tangible outputs that are linked with the steps outlined above for country deployment and implementation of ACTs:

- **Drug policy change:** Achieving this milestone will mean that different stakeholders, both within national governments and among partners, have reached consensus on making the decision to adopt ACTs.
- **Implementation planning completed:** At this stage, workplans will be in place and progress will have been initiated in the eight areas outlined in Section 1.1.
- **Drugs arriving in the country at the central level:** After a procurement cycle is successfully implemented, ACTs should start arriving in the country, which should be ready to distribute them to peripheral areas and to health facilities.
- **Drugs available to consumers in health facilities and communities:** This milestone means that drugs are starting to get to those who need them. However, monitoring and evaluation activities will be required to measure the achievement of this milestone.

1.3. Potential Bottlenecks

Anywhere along these critical steps, bottlenecks could occur, because each of the steps involves coordinated actions and collaboration among different stakeholders at the global and country levels.

1.4. RBM Partnership Contribution

Although leadership and initiative will be needed on the part of national governments to make the purchase of ACTs a high priority within their own budgets, external financial support will also be needed for many countries to purchase ACTs. Besides the Global Fund, other sources have been identified (World Bank 2003).

The process of mapping out resources available through the Global Fund and other sources should continue. This activity will require working with governments to identify money that could be available through SWAPs or other mechanisms. It will also require supporting National Malaria Control Programs and Ministries of Health in lobbying efforts to make the purchase of antimalarial drugs a high priority for national governments. Strategies to maintain adequate financing should be developed through these activities. Both specific delivery system strengthening and drugs are needed.

Subsidy mechanisms need to be developed and tested. A study released by the Institute of Medicine in 2004 will contribute to the development and implementation of different strategies for making ACTs affordable. Options include upstream financing, such as the use of public funding to purchase a stockpile of API that could be sold at a low cost to manufacturers for formulation into tablet form, and downstream financing, which would subsidize ACTs at the point of distribution to consumers. RBM Partners should support operational research in this area because it is likely that a variety of mechanisms will need to be used and adapted to each country's situation.

RBM Partners can support countries in other technical areas, of which the following is only a partial list:

- Supporting surveillance systems to collect reliable data on drug efficacy and disease incidence
- Reinforcing supply chain management to collect accurate consumption data and HMIS systems to collect accurate morbidity and mortality data; these kinds of data will be needed to generate accurate forecasts for use in procurement
- Strengthening management and technical capacity within countries
- Supporting development of effective procurement capacity and potentially implementation of pooled procurement

- Developing and reinforcing M&E mechanisms that will provide valuable information to National Malaria Control Program managers, Ministries of Health, national governments, and international partners
- Developing strategies for BCC to improve health care provider capacity and to educate consumers in better treatment-seeking behavior, the importance of compliance, and the use of combination therapy; these mechanisms could include a range of communications and marketing strategies, such as social marketing initiatives that have proven successful in family planning and ITN distribution as well as other marketing approaches

The list of tasks and responsibilities that are required at country level is lengthy and complex. RBM Partnership support will be available, but countries will have to take the initiative to start the process and to maintain the momentum necessary throughout the deployment and implementation process to ultimately ensure that their populations will have access to ACTs.

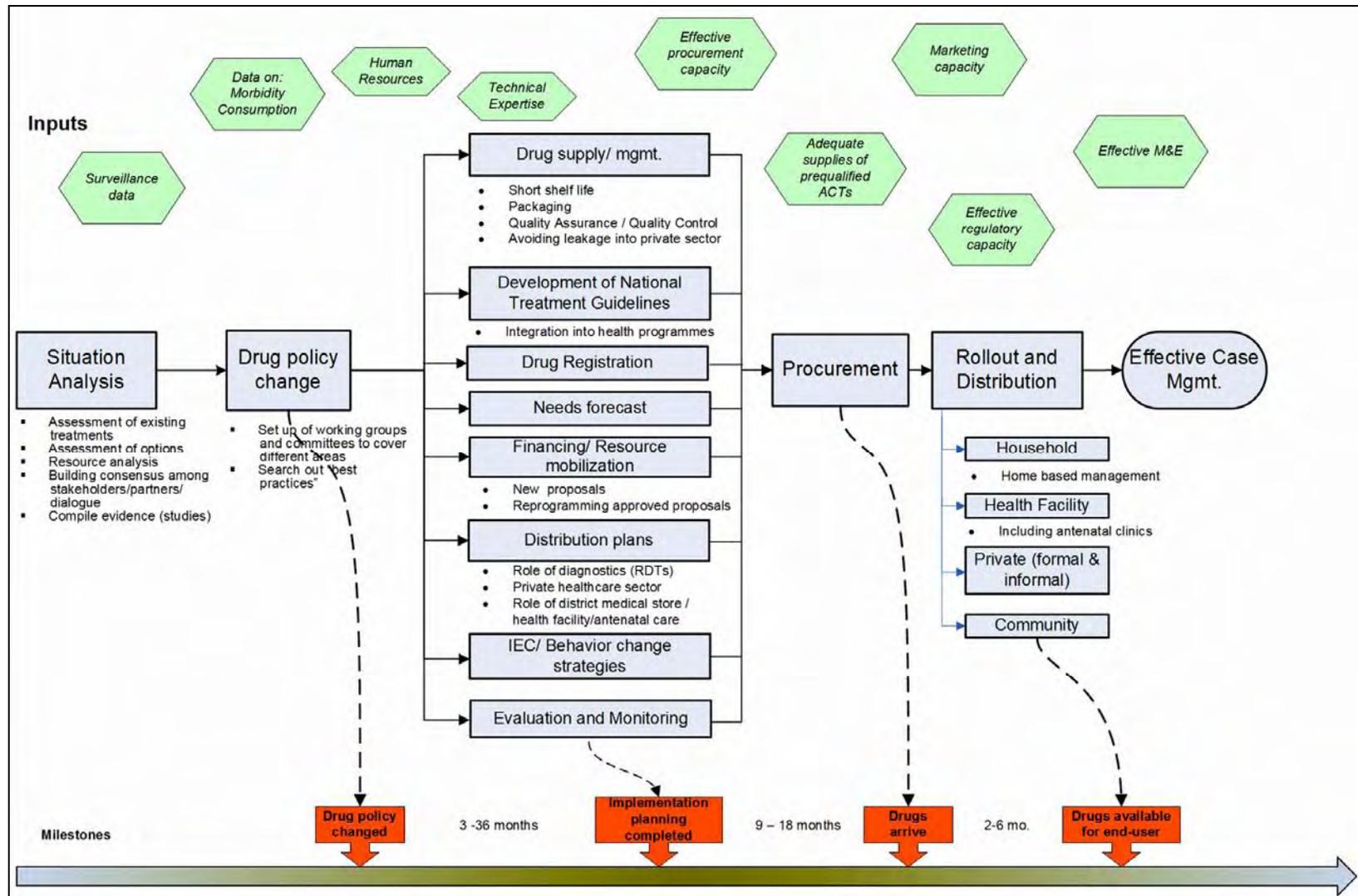


Figure 1. Country Deployment and Implementation of ACTs

2. Production of the API and Finished ACTs

2.1. Critical Steps

Several sets of critical activities should occur simultaneously to ensure an increase in the production of ACTs, including the following:

- **Increased production of the API using Good Manufacturing Practices (GMP).** This activity requires increasing the plantation of *Artemisia annua* and increasing extraction capacity to produce the API.
- **Increased production of API partner drugs such as amodiaquine.**
- **Increased manufacturing capacity for co-packaging and formulation of ACTs.** An ACT can require up to 24 pills and must be blister-packed because of specific age and weight dosing requirements, unlike many other essential medicines that can be packaged in bulk. The relatively short shelf life of ACTs also requires manufacturers to carefully manage their inventories of finished products.
- **Continued research and development of additional co-formulations and new molecules.** The roles of the Medicines for Malaria Venture (MMV) and the Special Programme for Research and Training in Tropical Diseases (TDR) are particularly important in this area because few private companies are likely to make the large investments needed to bring new molecules to market. Making new products (Table 2) such as synthetic endoperoxides available to consumers will require not only continued research and development but also planning for distribution and marketing, as well as pharmacovigilance activities to monitor the safety of the new drugs.

YEAR	EXPECTED PRODUCT
2005	Artesunate/mefloquine fixed-dose combination Artesunate/amodiaquine fixed-dose combination
2006	Artesunate/LAPDAP (chlorproguanil/dapsone) fixed-dose combination Artesunate/pyronaridine fixed-dose combination
2008	Artemisone combination? Synthetic trioxanes?

Source: Olliaro and Taylor 2003.

Table 2. Timeline for New Antimalarial Combinations

2.2. Milestones

From a public health perspective, ensuring competitive prices for ACTs will require an increased number of prequalified producers of both the API and finished ACT products, as well as an overall increase in production volumes, while research and development into new

co-formulations and new molecules continue. In summary, production-related milestones include the following:

- **GMP-quality supply of the API sufficient to meet demand.**
- **Increased number and geographic distribution of prequalified producers.** There is a strong desire to see African enterprises participate in the production of ACTs because eventually demand and consumption of ACTs in Africa will overtake these for the rest of the world combined. At the same time, ACTs that consumers will use should be of GMP quality.
- **Investments made in production capacity.** The large number of pills that are required for ACTs, and the requirements of packaging will require corresponding investments in production capacity.
- **Prequalified ACTs and suppliers sufficient to meet forecasts.**
- **New co-formulations and new molecules registered.** Discussions with industry, TDR, and MMV suggest that new ACT treatments will be available within the time frame covered by this road map.

2.3. Potential Bottlenecks

Intellectual property issues are not a consideration for a number of currently used ACTs because artemisinin-based medicines have been produced and manufactured for many years in Asia. However, the absence of an innovator brand (except for Coartem) that has met WHO prequalification standards means that investments in clinical trials may still be required, as well as investments in increased agricultural production of APIs and manufacturing capacity.

Increasing the Number of Prequalified Suppliers

To have more prequalified suppliers, two key things need to happen. First, ACT suppliers must make the investments needed to meet prequalification standards, and second, the WHO/UNICEF prequalification process should continue and be given sufficient resources. These issues can be addressed through actions by the RBM Partnership as outlined in Section 2.4.

Increasing the Supply of GMP-Quality API

Sufficient supplies of GMP-quality API appear to be available for 2004 needs, but few suppliers have been identified outside of China to meet needs for 2005 and beyond. None of the production sites in Vietnam have been prequalified by WHO, and plantations of *Artemisia* in Tanzania are still at the newly operational stage. The long lead time needed to grow *Artemisia* means that early communication of forecasts to growers and producers of the API is needed.

2.4. RBM Partnership Contribution

Several critical areas can readily be identified in which RBM Partners could support the acceleration of ACT production.

- **Including partners with expertise in agricultural production.** These partners could include UN-affiliated organizations such as the Food and Agriculture Organization or technical organizations such as Technoserve, which is active with coffee growers in Africa.
- **Compiling accurate country-level and global forecasts.** ACT producers have requested accurate forecasts, coupled with the assurance that financing will be available to pay for ACTs. A recent meeting with ACT manufacturers¹ has initiated a process of communicating available information via the RBM Partnership to manufacturers. This communication process, which the MMSS will continue, is valuable for creating the incentives needed for ACT producers to increase capacity and make the effort to reach GMP standards. Until the MMSS is operational, this work will have to be coordinated within the RBM Secretariat.
- **Developing packaging standards.** To avoid confusion, standard packaging and labeling requirements should be established so that health care providers and consumers do not become confused between the dosages and number of pills that are required for different age groups. A technical consultation on specifications for pre-packaging antimalarial medicines has taken place, and the specifications will need to be made operational.
- **Continuing collaboration with MMV, TDR, and other research initiatives.** Supporting the collection of data concerning both clinical efficacy and safety in field situations, along with strengthened systems for pharmacovigilance, will contribute to the data needed to establish safety of ACTs in pregnancy and for Phase IV data collection.
- **Exploring the possibility of low-cost financing for manufacturers who wish to expand.** Throughout sub-Saharan Africa, the high cost of commercial loans is often a deterrent to businesses that wish to invest and expand their manufacturing capacity. If ACTs are considered as a public good that should be made available at affordable prices to consumers, low-cost financing could help support African manufacturers who wish to invest in ACT production.
- **Technical assistance in meeting GMP standards.** Meeting GMP standards can be costly, and the development and documentation of standard operating procedures can be technically demanding. The availability of technical assistance could help catalyze additional manufacturers to reach these standards, thus diversifying the number of suppliers.

¹ WHO/UNICEF-hosted informative meeting of ACT suppliers, April 1–2, 2004, Copenhagen, Denmark.

- **Supporting the prequalification process.** The ACT market is characterized by the presence of only one product that currently meets International Conference on Harmonisation (ICH) standards. Various forms of artemisinin have been manufactured for many years in Asia without the benefit of the rigorous clinical trials that are typically required for approval in ICH countries. Therefore, the WHO/UNICEF prequalification process fills an important gap in this area and will be needed in the short to medium term to help guide countries in finding reliable ACT suppliers.

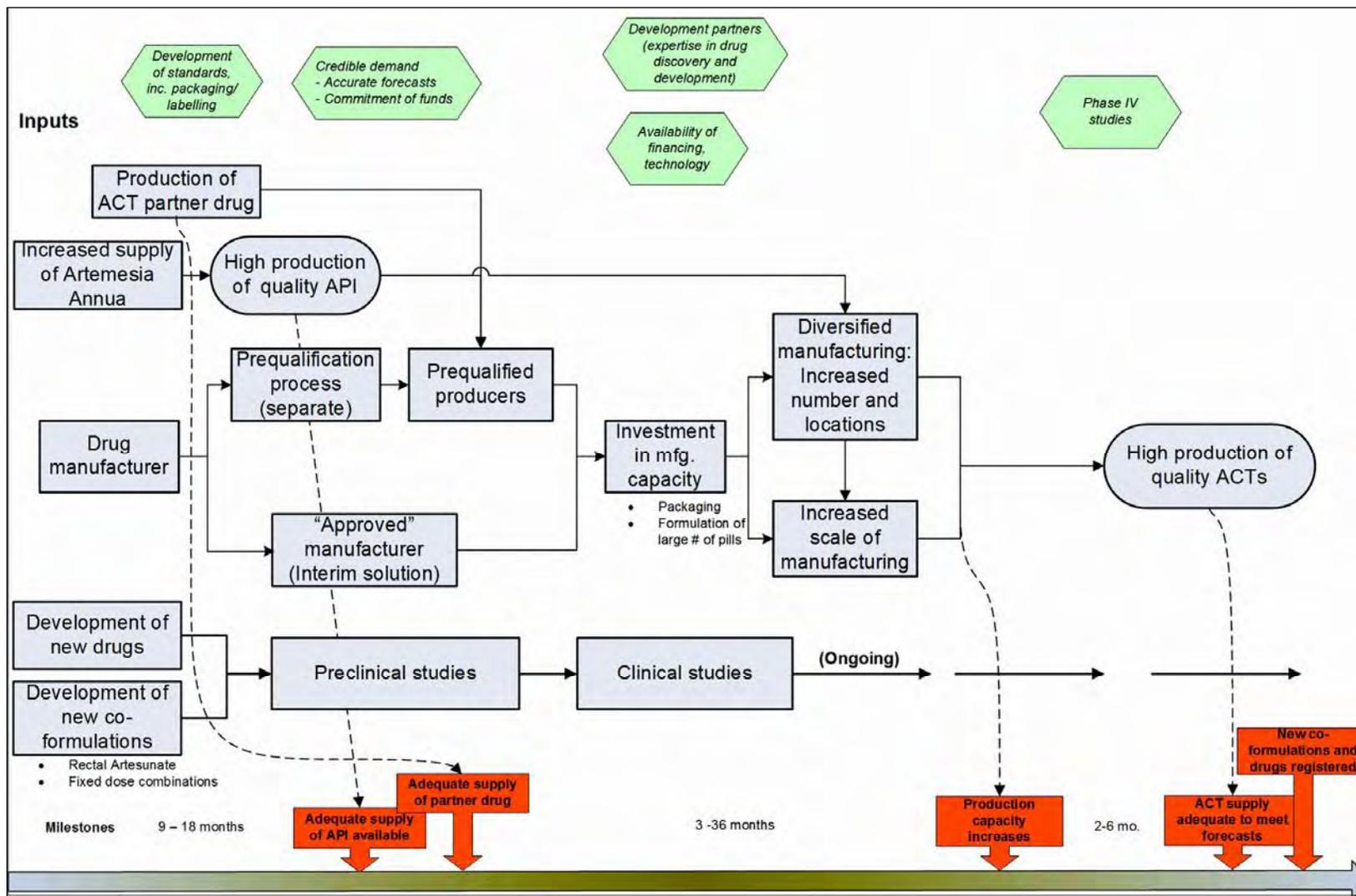


Figure 2. Production of ACTs

3. Procurement and Sourcing

3.1. Critical Steps

The procurement cycle for ACTs will have many elements in common with that of drugs and medical suppliers generally, but poses additional challenges for a number of reasons that include the high price of ACTs, the small number of prequalified suppliers, the lack of familiarity with ACTs, and their short shelf life (24 months for the finished product). For the purposes of this road map, a few critical steps are highlighted below. Fuller details of the steps of a procurement cycle can be found elsewhere (MSH/WHO 1997).

- **Selecting drugs.** The activities associated with these steps are addressed in Section 1.
- **Mobilizing financing.** For countries, the purchase of ACTs for the central medical store is likely to require resources outside the national budget. The Global Fund is likely to be a major source of external funding for countries, but with a cycle time of up to 12 months between proposal writing and disbursement, forecasts and planning have to be done early so that the procurement process can start.
- **Procuring ACTs.** With international competitive bidding (typically the method required by most donors), associated activities will include the publication of an Expression of Interest (EOI) and prequalification of suppliers, culminating in the delivery of drugs to the central medical store. The length of time typically required, which can be six months or more, is of particular concern for ACTs due to their short shelf life.

3.2. Milestones

The work streams that have to take place for the successful completion of a procurement cycle of ACTs include those directly related to the process of procurement as well as those related to financing. The discussion below focuses on the activities relevant to supplying the public and nonprofit sectors because the initial implementation efforts have focused on these sectors, where financing sources such as the Global Fund have been identified and where distribution systems are generally more transparent than those of the private sector. The milestones for each of these activities are listed separately.

Procurement Process

Milestones of the procurement process also include some financing and procurement cycle milestones, as specified:

- Drug policy has been changed.
- Accurate and precise forecasts of ACT demand have been made.
- Clear sources of financing are identified (see financing cycle).
- Procurement actions have been started (e.g., tenders issued) (see procurement cycle).
- Drugs are delivered to service delivery point (see procurement cycle).

Financing Cycle

- Sources of financing have been identified. National budgets, multilateral and bilateral institutions, NGOs, and foundations are resources that could be made available for supporting large-scale procurements at the national level. For illustration purposes, the next few steps below are specific for the Global Fund, although they may also be representative of steps needed for proposals to other donors.
 - Preparation and submission of a proposal.
 - Proposal approval.
 - Disbursement of funds. After approval, the Global Fund requires that receiving countries take steps toward implementation of management systems and development of a procurement plan.

Procurement Cycle

- EOI was published and tender documents prepared and issued.
- Suppliers have been prequalified.
- Proposals were received and evaluated.
- Awards were adjudicated.
- Drugs are delivered.
- Performance monitoring procedures are established.

3.3. Potential Bottlenecks

The need to coordinate activities that may be managed by more than one department or ministry increases the risk that financing activities may not be synchronized with the requirements of the procurement cycle, during which suppliers may require proof of credit before participating in tenders. Experience with early rounds from the Global Fund has shown that moving from grant approval to disbursement of funds requires extensive work to set up mechanisms of accountability, put in place procurement plans, and set up drug management systems. There is also a risk that separate drug management systems will be put in place to serve one set of drugs: this should be avoided, and where possible, existing systems should be strengthened.

3.4. RBM Partnership Contribution

The scope of activities that will take place for procurement and sourcing provides many opportunities for contributions, including the following:

- **Technical assistance with preparation and implementation of a financing proposal.** Proposal writing can be time consuming and can divert scarce human resources from the other crucial activities outlined above, including treatment guideline preparation and rollout and distribution of ACTs.

- **Strengthening procurement systems.** Pooled procurement of ACTs has been one mechanism suggested for ensuring that ACTs are of high quality and for providing incentives to ACT suppliers of guaranteed large purchase volumes while at the same time providing increased negotiation leverage to buyers. Putting these mechanisms in place requires coordination and careful planning.
- **Developing accurate forecasts.** Efficient procurement requires good forecasting. Accurate forecasting is likely to require the strengthening of drug reporting systems and HMISs.
- **Continuing the prequalification process.** Increasing the number of suppliers will help reinforce procurement processes.
- **Strengthening quality assurance systems.** QA activities include those at a global level, such as prequalification of suppliers and products, and those that take place on a regional/country level, such as support for the development of reference laboratories and direct support to national programs.

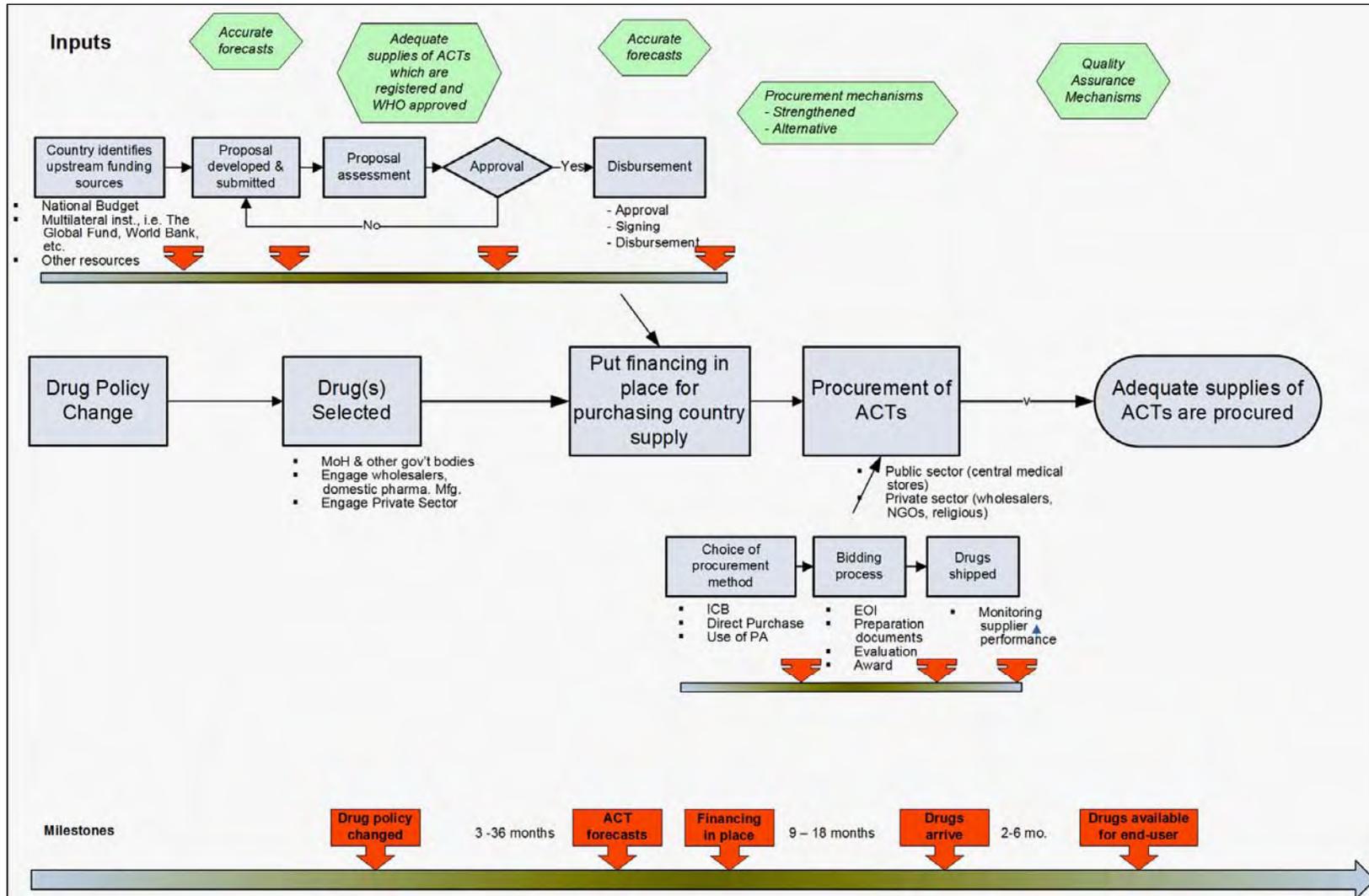


Figure 3. Procurement and Sourcing of ACTs

4. Distribution

To date, the few sub-Saharan African countries that have adopted ACTs have focused on distribution to the public sector and nonprofit private sector. As scale-up is undertaken, first, strategies for involving informal private health care providers need to be developed and the role and use of RDTs defined.

Second, ensuring that ACTs distributed to both public and private sectors are affordable is a high priority, and subsidies will be required. The Institute of Medicine study will provide valuable direction to the discussion of the merits and possibilities of both upstream and downstream subsidy mechanisms.

Third, ACTs will have to be implemented at the same time that existing monotherapies are phased out, which means that health care providers and consumers have to be retrained in the new treatment protocols while existing stocks of monotherapies are removed from circulation.

Fourth, supply chain management is critical to avoid wastage of these expensive products and to ensure that expired ACTs are removed from the supply chain and not distributed to consumers. Quality assurance activities need to be integrated throughout the supply chain.

4.1. Critical Steps

The critical steps correlate with the steps of distribution. These will differ in their details among countries, depending on how the public and private distribution systems are organized and whether central medical stores play a role in the distribution systems.

- Procurement at national level
- Storage at central medical store or private wholesaler (this will depend on the distribution system within each country)
- Distribution to regional medical store or private distributor
- Distribution to public health facility, including hospital, clinic, prenatal clinic, or community or private pharmacy/drug shop
- Distribution to end user/consumer
- Monitoring of efficiency of system and redistribution mechanisms

4.2. Milestones

- Drugs arrive at central medical store.
- Drugs move toward the periphery.
- Drugs are available in the community, health facilities, and drug shops.
- Most consumers, even vulnerable ones, have good access.

4.3. Potential Bottlenecks

Delays in the distribution system at any level, whether at central medical stores or at the peripheral level, could result in drugs being lost due to expiry, which is an increased risk with the short shelf life of ACTs. Leakage could result in drugs being diverted from their intended delivery to target populations.

4.4. RBM Partnership Contribution

Collaboration with countries in developing and implementing viable distribution plans, in ensuring that the shelf life of ACTs is respected, and in integrating quality assurance activities with distribution activities will include the following:

- Technical assistance in developing distribution plans
- Developing, testing, and deciding on subsidy and cost-recovery mechanisms
- Technical assistance in establishing laboratories for quality control
- Training in supply chain management

Monitoring and evaluation activities should be integrated with these activities, both for donor feedback and for the operational research that will be needed.

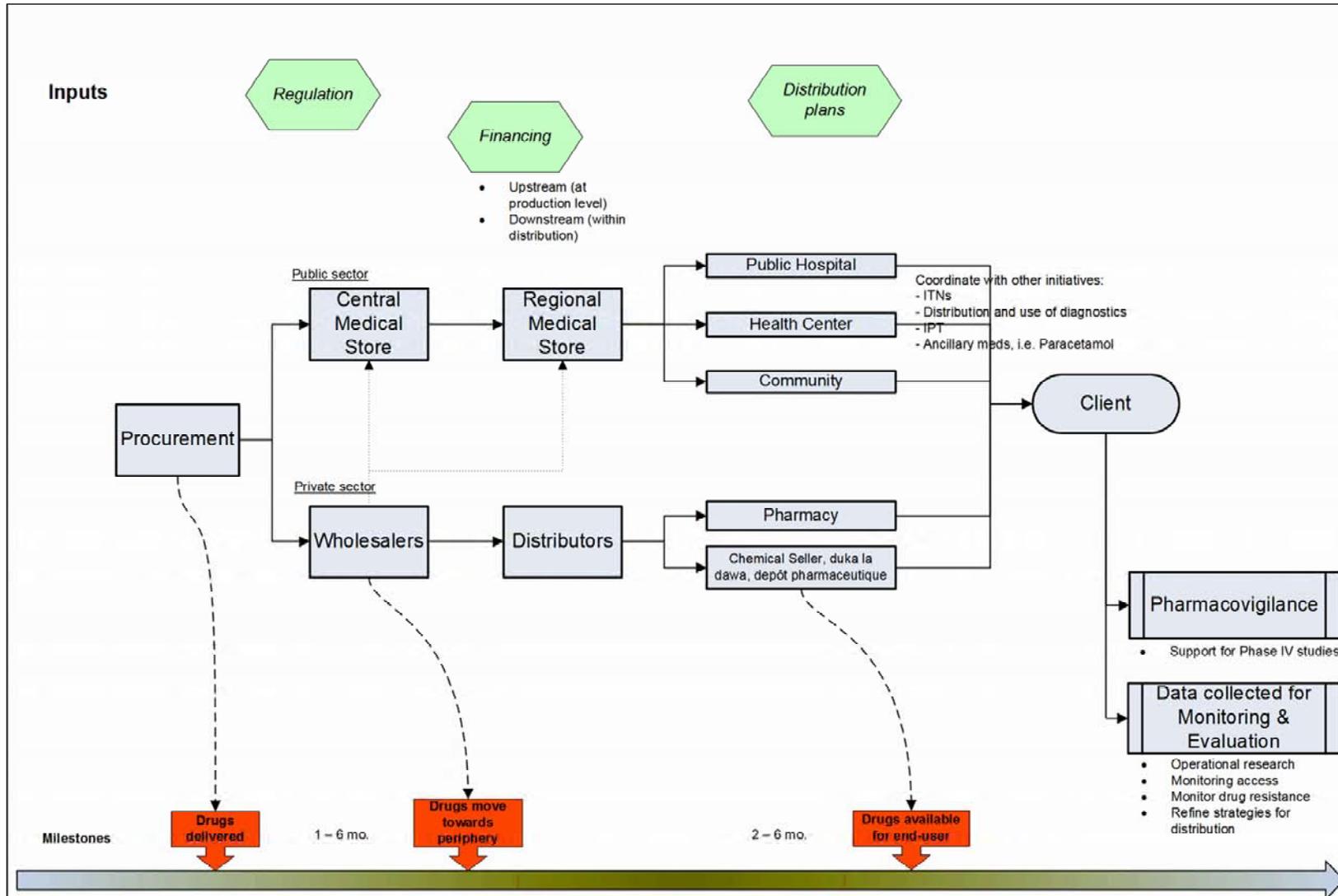


Figure 4. Distribution of ACTs

5. Prequalification

The importance of the prequalification process has been discussed above because of its impact on production and procurement. The WHO/UNICEF prequalification project for ACTs has been under way since the first EOI was published in May 2002 and is managed by the Quality Assurance and Safety of Medicines (QSM) team within WHO/EDM. Two products from two suppliers have been prequalified to date: Coartem and artesunate.

The steps of prequalification are similar to those of typical registration procedures, including drafting of specifications and guidelines for products and product dossiers, publication of an EOI, evaluation of the dossier, site inspection to confirm compliance with GMP, and analysis of product samples. The final step of a successful prequalification process is inclusion on the published list of suppliers for procurement purposes. An additional benefit of the WHO/UNICEF prequalification project is the strengthening of country regulatory systems.

5.1. Critical Steps

The prequalification process takes 2–12 months, which is largely determined by response time of the applicants, and requires ACT suppliers to submit comprehensive dossiers including pharmacology, toxicology, and clinical efficacy studies and bioequivalence studies (where appropriate). The process is well documented elsewhere (WHO 2004).

5.2. Milestones

Milestones are straightforward to define, based on the steps of the prequalification process:

- EOI published
- Dossiers submitted
- Inspections performed
- Evaluations completed
- Products prequalified and on list
- Producers prequalified

5.3. Potential Bottlenecks

Successful completion of the prequalification process requires that dossiers submitted by manufacturers be complete and that site inspections be performed. These activities can be accomplished in as little as three months if the documentation is in order. Delays in documentation or a lack of qualified inspectors to visit manufacturing sites will slow the prequalification process. Potential bottlenecks in the prequalification process can be summarized as follows:

- Dossiers that are not ready for evaluation
- Clinical efficacy and stability data that does not meet standards

- Lack of comparator product, which means that showing bioequivalency is insufficient for prequalification
- Few qualified manufacturers responding to the WHO/UNICEF EOI

5.4. RBM Partnership Contribution

Beyond supporting the WHO/UNICEF prequalification project directly, additional support, some of which includes activities that have been discussed above, could include the following:

- Development of a reference standard
- Technical assistance to ACT suppliers to help meet the GMP standards
- Low-cost financing to ACT suppliers, especially small African enterprises, to help them improve quality, in return for guaranteed prices

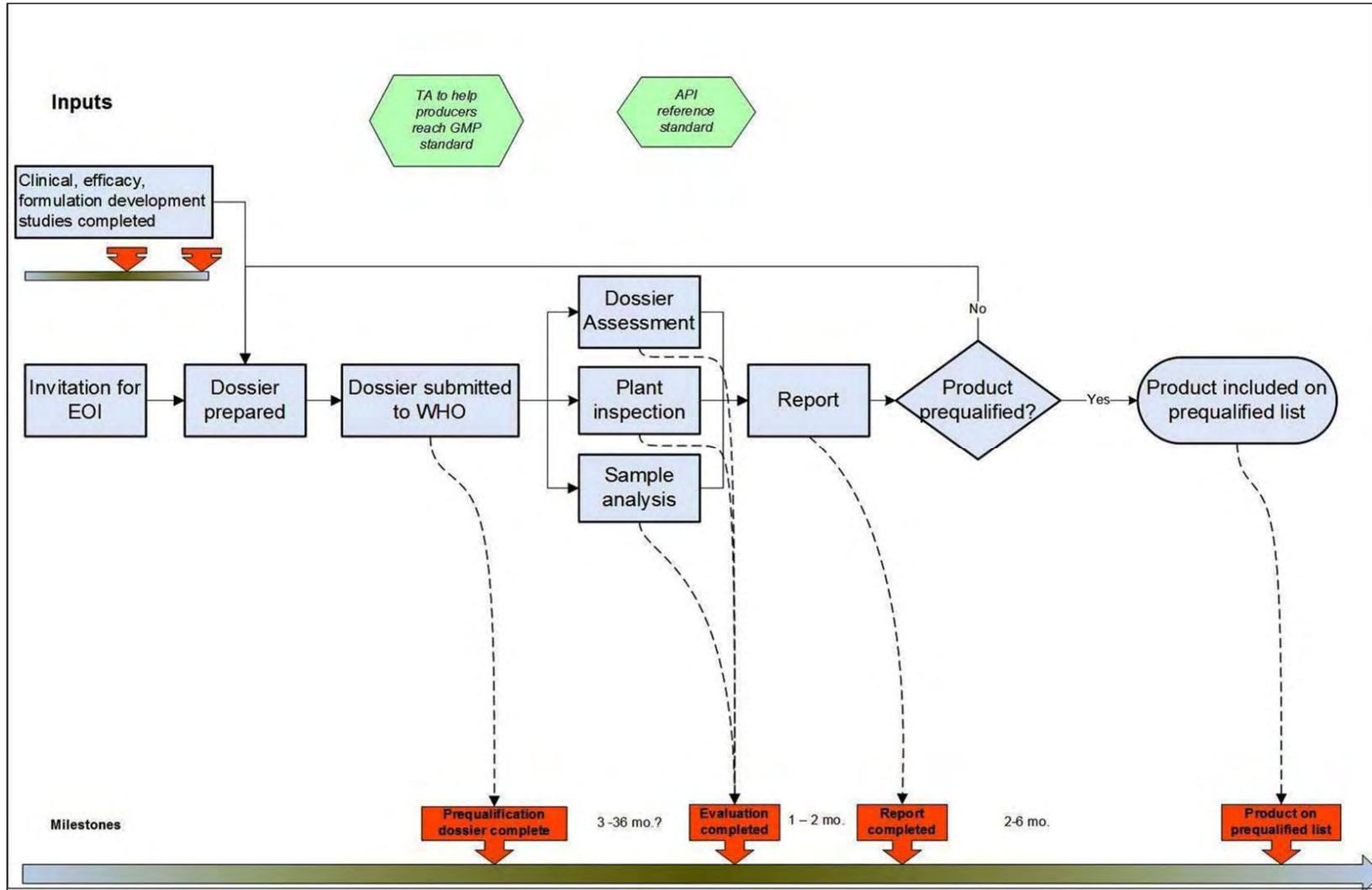


Figure 5. WHO/UNICEF Prequalification of ACTs

6. Registration and Regulation

Registration is a fundamental step required by countries before they allow ACTs to enter the country and be integrated into the health system. However, many countries do not have robust registration systems or a strong regulatory system, which has led to a proliferation of nonapproved, poor-quality products in many countries. Besides the issues of quality and safety that this lack of adequate regulatory control poses, the uncontrolled use of monotherapy forms of artemisinin and its derivatives and of inappropriate ACTs could eventually lead to resistance.

6.1. Critical Steps

Drug registration should follow a process similar to that of the WHO/UNICEF prequalification scheme, including dossier submission, site inspection, and a regulatory decision. In addition, countries need to make scheduling decisions for ACTs, that is, decide whether to make them available only through prescription at licensed pharmacies or whether to allow them to be distributed by the small vendors prevalent in many sub-Saharan African countries, such as *dépôts pharmaceutiques* or chemical sellers.

6.2. Milestones

The list of milestones parallels those for the prequalification process, including the following:

- Dossiers are submitted.
- Dossiers have been evaluated and site visits performed.
- Regulatory approval has been obtained.
- Scheduling decisions have been made.

6.3. Potential Bottlenecks

Besides the types of difficulties that could be encountered in the prequalification process, additional delays could include the following:

- Country requirements for clinical efficacy studies performed in that country
- Lack of human resources to evaluate dossiers, leading to backlogs

6.4. RBM Partnership Contribution

Reinforcing regulatory agencies will help protect the public against substandard products. This issue is crucial because the high price of ACTs is likely to create an increased risk of counterfeits, which are already a well-known problem in many countries (WHO/EDM 1999). The partnership could support these activities in several ways:

- Training activities for regulatory agency personnel in technical areas and in management
- Establishing international, independent reference laboratories in Africa for quality control testing

- Establishing guidelines on regulation enforcement
- Collaborating with countries to develop databases of market data so that regulatory agencies are aware of what products are on the market
- Establishing an independent database of products that have been determined to be counterfeit

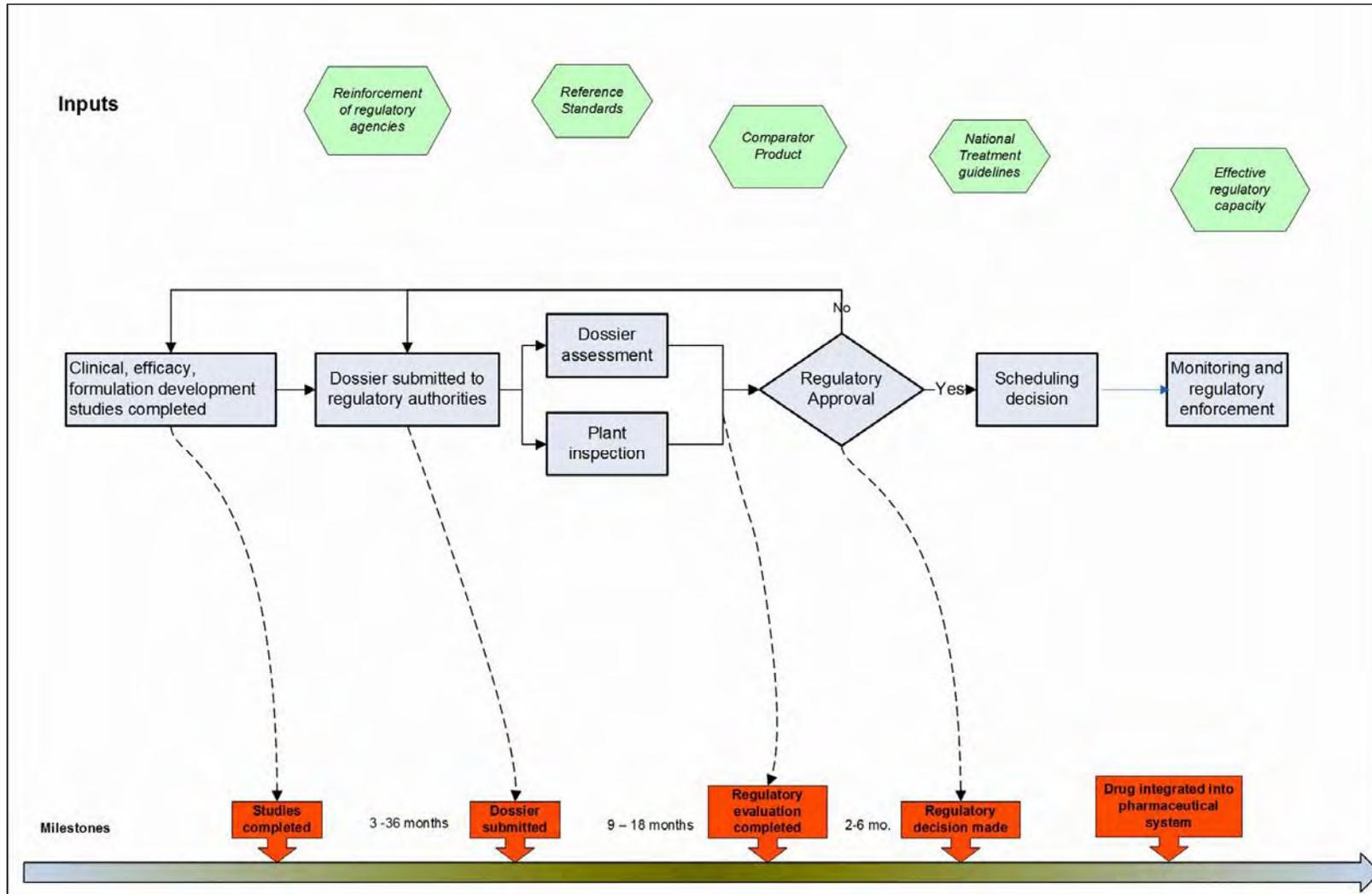


Figure 6. Registration Process for ACTs

Conclusion and Next Steps

Making ACTs accessible to those who need them provides opportunities and challenges for many areas of the health sector, ranging from those that require social science expertise, such as information and communications, to those that require specialized technical expertise, such as research and development (see Annex 2). Making this strategic plan operational will require coordination among various stakeholders. Collaboration among different specialties will be necessary in each country and at the global level. The MMSS will be able to carry out or coordinate many of the activities described above. For those activities that do not fall within the scope of activities of the MMSS, as well as for those activities that are urgently needed to meet the needs of 2004, the following steps are suggested:

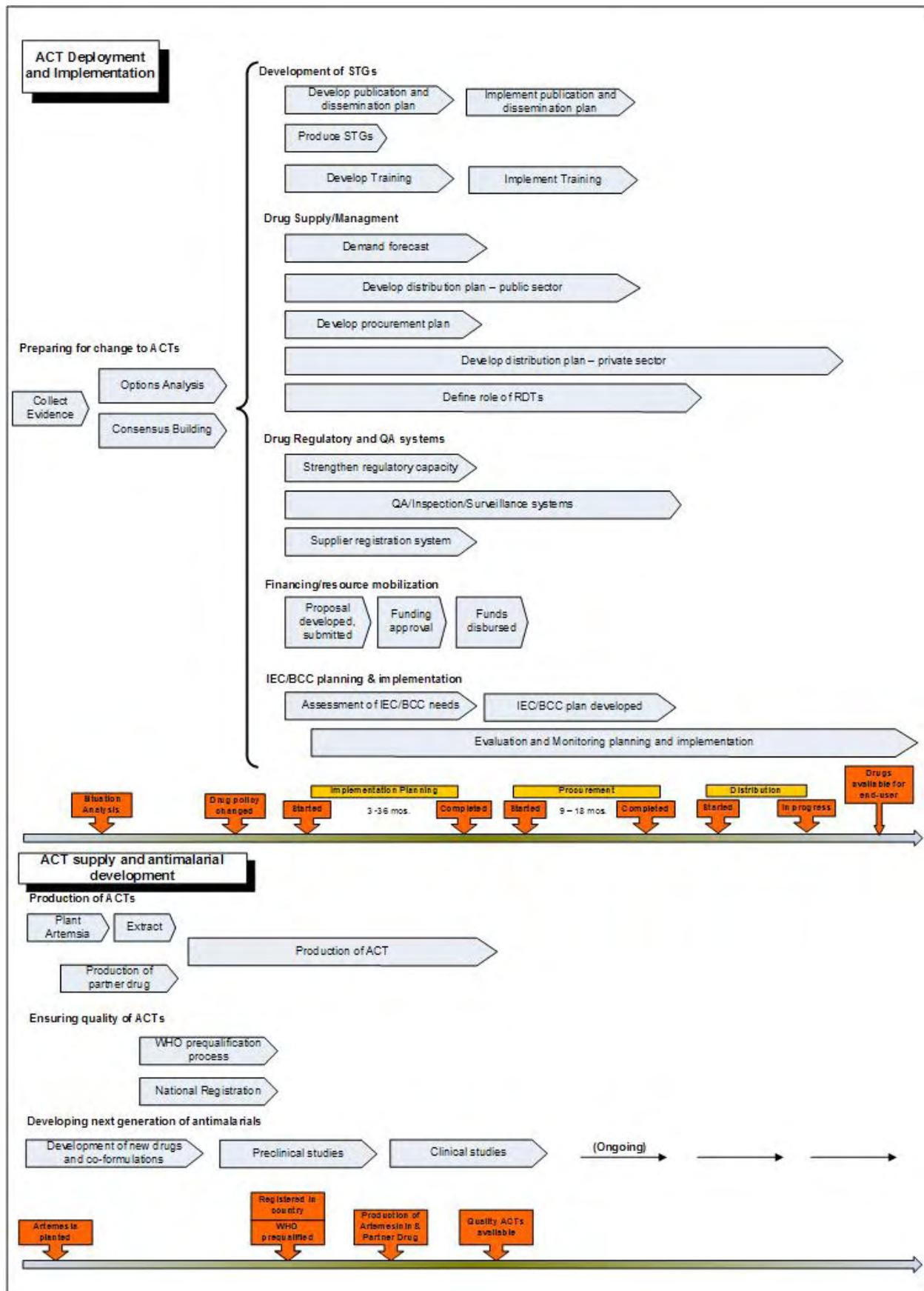
- Task the RBM Secretariat with defining the roles of the various RBM Partners that are necessary to operationalize the strategic plan
- Define a set of strategies for ACT distribution through the private sector.
- For those countries that have adopted ACTs or will adopt them in 2004 as first-line treatment for malaria and that are also RBM focus countries, ensure support for the planning and implementation of drug policy change
- Develop guidelines for the use, procurement, and supply chain management of RDTs
- Establish a working group within RBM to make the road map operational; ideally this group should include representation from the Secretariat, the WHO RBM Department, and key RBM Partners

Because of the urgency of working with those countries that are actively grappling with the issues of ACT implementation and the need to address the potential gaps in financing and procurement that have been identified, the list of activities developed as of April 2004 to meet immediate needs in this year is resummarized in Table 3.

Global-Level Activities	Country-Level Activities
1. Identify additional suppliers of acceptable-quality ACTs	1. Map out resources in each country from funds already approved or disbursed by the Global Fund in Rounds 1–3 and other sources that could be made available to purchase ACTs
2. Continue the prequalification process	2. Work with countries to ensure that appropriate requests are made for ACTs in future Global Fund proposals
3. Compile a list of sources and prices that includes information on ACT suppliers	3. Gather information on implementation and rollout plans, with associated timelines, for those countries that will be moving to ACTs in 2004
4. Make MMSS operational	4. Match the resulting requirements for ACTs against available funding through the mechanisms highlighted above
	5. Develop implementation and rollout plans specific to each country's environment

Table 3. Global- and Country-Level Activities

Annex 1. Graphical Presentation of Road Map



Annex 2. Research Agenda to Inform and Monitor the Scale-Up of Artemisinin-Based Combination Treatments

There is a growing momentum to go to scale in the implementation of ACTs in malaria-endemic countries, particularly in Africa. A road map intended to facilitate collaboration within the RBM Partnership to meet short- and medium-term needs of countries that have or will soon adopt ACTs requires a research component that can assist, facilitate, and inform this scale-up.

With the scale-up of ACT now becoming a reality, this is the right time to develop and communicate widely an implementation research agenda related to ACTs. This activity will require a review of current activities in order to identify gaps, an agenda that informs and monitors the scale-up of ACT in a more comprehensive manner, the definition of a realistic plan of action, and the need to work through partners and RBM to raise funds to support this important effort. TDR is in the process of initiating a meeting on behalf of the RBM Partnership to address this issue.

Several countries have included in their Global Fund proposals requests for funds for operational research. It is important that these country-level efforts are provided with appropriate support and direction for them to be scientifically sound, especially in countries where research capacity is weak. The efforts also need to be coordinated in such a way that there is cross-country sharing of experiences and duplication is avoided.

Research involving many partners and largely coordinated through TDR was instrumental in providing the evidence that has led to WHO's recommendation for ACT. Much experience has been gained in recent years from "proof-of-principle" studies and "implementation research" projects whose results can assist in achieving optimal outcomes with scale-up of ACT. In the other sections of the road map, the role of drug development was well highlighted and recognized as central to the whole ACT effort. The significant role of the more downstream types of research needed to inform implementation is often not so well recognized and needs more comprehensive development and advocacy.

In several places in the road map document, issues that relate directly or indirectly to implementation-type research are alluded to. These issues include the following:

- The need to define the role of diagnostic aids, taking into account local or regional malaria prevalence
- The need to develop and test strategies for implementing ACTs in the private for-profit sector
- The need to develop and test subsidy and cost-recovery mechanisms
- Appropriate IEC that will lead to measurable behavior change
- Mechanisms for enhancing compliance to the multiple dosing with large numbers of tablets needed for ACTs

- The research necessary to speedily introduce new and unfamiliar drugs into care delivery systems that reach communities and homes
- Accelerated Phase IV–type research coupled with establishment of pharmacovigilance systems, and evidence of clinical efficacy in field situations
- Safety of ACTs during pregnancy
- ACTs in settings with high HIV prevalence
- ACTs in very young children and underweight, malnourished children
- Practical issues related to the short shelf life of ACTs, such as retrieval of expired drugs, incentives for not using expired stocks, and how to avoid wastage of ACTs
- Questions that may emerge from monitoring and evaluation
- Monitoring the markers and the development of resistance caused by uncontrolled use of monotherapy artemisinin and inappropriate use of ACTs
- Country-specific clinical efficacy trials for ACTs

In addition to the importance of having a research agenda that includes the elements outlined above, together with the efforts to implement ACTs, it should be acknowledged that there is already substantial research being undertaken in some of the areas mentioned in the road map. However, these need to be expanded and established within a broad strategic framework. Some examples are given below:

- Clinical trials of ACTs
- Effectiveness assessment of ACT implementation in scaling up (SEACAT, Zanzibar, Senegal, Brazil)
- ACTs in home management
- Multilateral Initiative on Malaria (MIM)/TDR Antimalarial Drug Resistance Network
- Other research capability strengthening activities such as capacity building for good laboratory practices and good clinical practices
- Lessons that can be learned from TDR’s work on the LAPDAP Phase IV program
- Seeking of funds to develop and test a strategy for more comprehensive management of febrile children in whom malaria coexists with pneumonia

Meeting to Define the Agenda

TDR, on behalf of the RBM Partnership, will arrange a two-day meeting at the beginning of September 2004, inviting relevant partners and scientific experts to review ongoing research on ACTs and redefine the research agenda.

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Additional Resources

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