Lapdap™ Antimalarial Drug: GlaxoSmithKline, WHO-TDR, and the U.K. Department for International Development

Lapdap™ is a new combination of two off-patent malaria drugs. The U.K. Medicines and Healthcare Products Regulatory Agency approved the drug in 2003 for the treatment of malaria caused by *Plasmodium falciparum*, which kills one to two million people every year. The combination drug was developed in response to the growing resistance among patients to malaria drugs, with failure rates in Africa as high as 40 percent.

Lapdap came out of early research funded by the Wellcome Trust and was brought to market by a public-private partnership (PPP) involving GSK (GlaxoSmithKline), WHO-TDR (a WHO/UNDP/World Bank Special Program in Research and Training in Tropical Diseases), and the U.K. Department for International Development (DfID). This was done in collaboration with scientists from the University of Liverpool and the London School of Hygiene and Tropical Medicine, African researchers and clinicians, and the Wellcome Trust.

Under the terms of a funding partnership, GSK, WHO-TDR, and DfID each paid one-third of the development costs. Their agreement covered the ownership of nonpublished data and the establishment of a product-development team to continue development and obtain regulatory approval.

Early patent applications filed on the basic biological work underlying the combination of the two existing drugs were abandoned after filing because it was later found that the work had already been published in scientific literature and so there was 'prior art.' There are currently no patents protecting the Lapdap™ product in any country.

Lapdap™ was developed to be as inexpensive as possible, with a public sector target of less than US$0.30 per dose. It is currently sold only through private sector pharmacies, with the commercial sale price varying by country. The drug is available in South Africa, Nigeria, Kenya, and Ivory Coast.

Lapdap's™ role in public health is still being assessed; Phase IV studies are ongoing and the WHO has stated that after reviewing available clinical and preclinical data, it will identify strategies for optimal and safe use. Lapdap™ has potential for future public health initiatives; a collaborative agreement was signed in April 2004 between GSK, WHO-TDR, and MMV to develop a new fixed-dose artemisinin combination-therapy drug combining chlorproguanil, dapsone, and artesunate for treatment of malaria.

Successful collaboration to ensure that developing countries benefit from the fruits of intellectual property requires an integrated approach toward networking and capacity building, involving innovation, regulatory approval, market creation, licensing, and distribution.

The lack of formal health infrastructure in rural Africa, where there are few physicians and where the drug is sold over the counter, has led to great importance being attached to the packaging and distribution, as well as education to ensure proper dosage. The establishment before registration of a public health group, under the WHO's auspices, provided a useful forum for discussing how Lapdap™ would be accessed. This case highlights the need for consensus regarding

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Editors' Note: An earlier version of this case study was presented at the MIHR conference Using Intellectual Property for Improved Health in Developing Countries: An Evidence-Based Approach to Good Practice, Bellagio, Italy, June 14–18, 2004.

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public sector use of the product between all parties involved in national malaria control.

This case study was considered 'IP neutral,' since the academic and public health mission was neither impeded nor driven by IP considerations. However, the Wellcome Trust, as part of its mission, recognizes the important role of industry and its investors (including non-commercial funders) in translating research innovations into new health products. It therefore encourages and supports the responsible use of IP rights to protect research findings where commercialization or further funding which could benefit from the existence of that underlying IP is necessary to achieve the greatest public benefit.

It could be argued that the lack of underlying intellectual property in this case, specifically patents, may have accelerated the research project and reduced transaction costs. On the other hand, the absence of patents may have slowed this process, particularly the attainment of Phase IV studies because a patent-driven time schedule did not drive the development process.

It was generally agreed, however, that intellectual property other than patents was generated in the form of regulatory dossiers (clinical trial data), know how, terms of codevelopment agreements, and trademarks. Recognizing the multiplicity of intellectual property can contribute to a more comprehensive understanding of the IP management aspects of product R&D, post-development, and manufacturing.

Lapdap's™ pursuit of WHO endorsement raised the broader policy issue of the global health body's role as a certificatory of treatment regimes. WHO approval is a vital step in products reaching developing countries and gaining public sector acceptance. However, responsibility within a PPP for securing such endorsement is not always clear.

Regulatory endorsement is but one aspect of product sustainability. Royalty streams should be examined for how their use and management can contribute to product support. Although often treated as undesirable additional costs, the generation of royalties on public sector sales is an effective IP management tool for keeping a product on the market.

The involvement of universities in this public health initiative drew attention to the role of university technology transfer offices (TTOs). It appears that TTOs are frequently given competing missions by their institutions, with no clear priority as to whether making money or delivering applications of research regardless of returns is the most important goal. Declining revenue of universities has pressured cash-strapped TTOs to increase their contribution, compelling them to turn to intellectual property. Although exploiting university research is a legitimate goal, it may be short-sighted to focus solely on patents; the transfer of know-how and trade secrets is just as important, and an overemphasis on revenue generation using IP rights may limit the potential of certain research outcomes.

In attracting commercial interest, TTOs must be mindful of overvalued patents and overestimated royalties, and must know how to manage hurdles and prevent unreal expectations. Alongside the need for flexibility in negotiations, education about technology management is required.

The challenge therefore is to use PPPs as an effective means of bringing drugs to the poor by drawing on the expertise and synergies between sectors. These partnerships afford the opportunity to segment the market in a way in which the public body can benefit from having an exclusive license for its stakeholders while satisfying commercial partners.

TYPES OF AGREEMENTS

An agreement was signed relating to establishment of the product-development team and ownership of nonpublished data. Under the funding partnership between GSK, WHO-TDR, and the U.K. DfID, each partner contributed one-third of the development costs.

PATENT AND IP RIGHTS DECISIONS

Early patent applications were filed between 1994 and 1996 by GSK (then SmithKline Beecham) on the basic biological work underlying the combination of the two existing drugs, with Dr. Bill Watkins (University of Liverpool & Wellcome Trust Research Laboratories, Kenya) as named inventor. These applications were later abandoned, because after filing it became clear that the combination had already been published in the literature and therefore was no longer novel. There are therefore no patents protecting the Lapdap™ product in any country.

POLICY IMPLEMENTATION

Lapdap™ at present is being sold only through the private sector (pharmacies). WHO does not currently recommend the use of chlorproguanil-dapsone alone as an option for national treatment policy in countries where malaria is endemic. The role of the drug in public health is still being assessed—Phase IV studies are ongoing, and pharmacovigilance activities in specific patient groups are planned. WHO has stated that after reviewing available clinical and preclinical data, it will shortly identify strategies for the optimal and safe use of Lapdap™ in malaria-endemic countries.

Because of Lapdap's™ reported efficacy, relatively short half-life, and low production cost, it has potential for future public health use in combination with an artemisinin compound. In April 2004, a collaborative agreement was signed between GSK, WHO-TDR, and MMV to develop a new fixed-dose artemisinin combination-therapy drug combining chlorproguanil, dapsone, and artesunate for treatment of malaria.

EXTERNAL FACTORS THAT AFFECTED DECISION MAKING

In the case of Lapdap™, where IP considerations did not drive the later development of the project, some external factors of relevance were:

- nature of the end market for Lapdap™ (poor countries in Africa)
- multiparty cooperation and synergy

KEY LESSONS AND HEALTH-ACCESS ISSUES

The following lessons were learned during development of the Lapdap™ drug and subsequent distribution:

- Pharmaceutical industry expertise in clinical trials, the regulatory process, and marketing are necessary to accelerate product development.
- Establishment of a public health group under WHO auspices *in advance of registration* was a useful forum for discussing how the product would be accessed.
- Consensus on the use of the product in Africa is necessary at the country level between parties involved in malaria control. ■

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