

## PERSPECTIVE FOR THE PRODUCTION OF ANTIMALARIAL DRUGS IN BRAZIL

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*There appears to be no chemical manufacture of antimalarial drugs in Brazil. Technology at the laboratory process level has been developed for chloroquine, mefloquine, pyrimethamine and cycloquanil, but not perfected nor scaled-up, largely for economic reasons and market uncertainty. Development of primaquine has been contracted but it will run into the same difficulty. Manufacturing capacity for sulfadoxine was registered in the SDI by Roche. A project to produce artemisinin and its derivatives is under way at UNICAMP-CPQBA but is hampered by low content in the plant. Proguanil could be produced easily, but apparently no attempt has been made to do so. Quinine is imported on a large scale mostly for softdrink production.,*

*Since malarial treatment falls largely within the responsibility of the Government health authorities, manufacture of drugs in Brazil will depend on an assured medium-term purchase order made to a potential local manufacturer, since competition in the world market is scarcely viable at the present moment.*

Key words: anti-malarial drugs – chloroquine – mefloquine – pyrimethamine – cycloguanil – artemisinin

Brazil has the biggest population exposed to malarial infection in the Americas, and for strategic reasons it would seem that the manufacture of drugs for its combat in the country would be a logical part of a national health programme. The treatment of malaria is largely a Federal responsibility, so that the Ministry of Health bears the main responsibility for making the necessary drugs available just as it is also responsible for most of the vector control. There is always a risk of interruption of supplies, when these depend on Government importation, and it would be a simple precautionary measure to manufacture one or two of the more important drugs in the country, even at a modest financial loss. This has been the policy followed by India and China. The private sector will never show firm interest in the manufacture of drugs which can be imported more cheaply than they can be manufactured, especially when: (I) Importation is becoming progressively easier, and (II) the official Drug Agency may opt at any moment to import a drug, even when the technology for manufacture of that drug was developed under its auspices and with its financial support.

The fact that there is no certainty of sale inhibits manufacturing initiatives and while this

uncertainty remains, the situation is unlikely to change.

Chloroquine and the chemically related amodiaquine are probably the most consumed antimalarials, although a large number of *Plasmodium* strains have a defense mechanism against this type of drug. The defense mechanism shows the characteristics of a multi-drug resistance phenomenon mediated by a transmembrane glycoprotein and reversible by a number of drugs, among them calcium channel blockers (Martin et al., 1987; Krogstad et al., 1987; Bitonti et al., 1988). If the concomitant use of such a blocker were introducible as a valid therapy for malaria, chloroquine could rapidly regain its prominent position.

Production of chloroquine from two imported advanced intermediates could be installed rapidly. Manufacture of the intermediates requires quite a large investment which would effectively never be recovered at present levels of use, so that verticalization would have to await a larger market. The final stages of chloroquine diphosphate production were executed in the laboratory (CEME - Instituto de Pesquisa da Marinha - IPqM) and many of the

earlier stages have also been reproduced on this scale (CEME - IPqM and Far-Manguinhos).

Amodiaquine is derived from one common advanced intermediate - 4,7-dichloroquinoline - used in chloroquine manufacture. It has also been the subject of a CEME-financed development project (CEME-Formilquímica) and again could be produced at relatively short notice from imported intermediates. Since amodiaquine is not a recommended drug in some countries, e.g. UK, because of the high incidence of agranulocytosis associated with its use, preference should be given to chloroquine in a decision to manufacture.

Of the dihydrofolate dihydrogenase inhibitors, pyrimethamine, proguanil, and cycloguanil, the dosage used with pyrimethamine is lower, which probably means lower side effects, so that it is considered the drug of choice. However, the two alternative drugs proguanil and cycloguanil are very easy to make and merit attention. ICI produces proguanil although it is not apparently marketed by any pharmaceutical distributor in Brazil. It has proved a useful drug in some locations in the north. Cycloguanil, once a Parke-Davis product launched in a deposit formulation for prophylaxis, seems to have disappeared from the market. One might suppose that in view of the renewed interest in proguanil that this drug could merit re-examination, not as a deposit formulation, but as an oral prescription. It would be an ideal product from the chemical manufacturing point of view. Both pyrimethamine and cycloguanil have been synthesized in the laboratory locally (Far-Manguinhos & IPqM respectively) and could be produced industrially. Of the two cycloguanil would be much cheaper.

Primaquine is under-employed in malaria treatment in the north. The common use of chloroquine-tetracycline and quinine-pyrimethamine regimes seems to leave a large number of human transmitters of *P. vivax* in circulation, whose treatment with primaquine could have produced radical cure. The small consumption of primaquine taken together with the length of its synthesis, preclude manufacturing at the present time.

Mefloquine, on the other hand, is obtained by a considerably shorter synthesis than

primaquine, and is a drug largely free of the resistance phenomenon associated with other drugs. Its price would probably justify its manufacture and should be seriously considered. It can be used both for *P. falciparum* and *P. vivax* infections, but great care would have to be exercised to prevent the type of misuse (especially in prophylaxis) that has facilitated the spread of strains resistant to other drugs. The synthesis has been executed in the laboratory (Far-Manguinhos) and its repetition at a production level - quite small for mefloquine - would not be expected to present difficulty.

The related drug, halofantrine, has not, to the knowledge of the author, been synthesized in the country and therefore no prediction can be made as to ease or cost of production.

The sulfa-drug sulfadoxine is commercialized in two forms, one a tablet, the other an injectable formulation with associated pyrimethamine. Synthesis from imported advanced intermediates offers no special difficulty and the process is registered in the Secretaria de Desenvolvimento Industrial. The sulfonamide moiety also offers no difficulty as an intermediate and its use in multiple other sulfa-drugs make its manufacture viable but manufacture of the pyrimidine moiety is not economically feasible due to the small consumption. Sulfamethoxypyrazine (sulfalene) is also offered on the local market. The same drawback applies to the pyridazine moiety of this drug. Neither are very important in the global picture it seems.

Turning to natural products, two groups of products come to mind - one old, comprising quinine as sulphate (oral) or dihydrochloride (injectable but hazardous), and one new, comprising artemisinin, artusenate and arte(m)-ether. The production of both are agronomical and not chemical problems. Both plants *Cinchona ledgeriana* and *Artemisia annua* have been planted in Brazil, and both have failed, according to report, to produce useful quantities of the antimalarial. Modern genetic methods would permit this problem to be solved, but so far, in the case of *Cinchona*, sufficient interest has not been forthcoming. Quinine is a commodity and therefore sales must meet all markets - soft drinks as well as medicines. Prices will always be low. In the case of *Artemisia* it is still early. Of two strains planted as seeds in Campinas, one was reputedly a sat-

isfactory one in terms of artemisinin content, but under the excellent soil and climate conditions of the University grounds, the plant appears not to "need" this secondary metabolite. The artemisinin group antimalarials are, with the exception of artusenate, injectable drugs. This is not very convenient. It remains to be seen whether other plant remedies for malaria can be brought to clinical use. Like *A. annua*, all are oral drugs in their popular use and they are worthy of development as possible solutions to the problem of malaria control in remote areas where mortality arises more due to the *local* non-availability of antimalarial drugs than to their national shortage.

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