THE ROLE IMPACT AND ORGANIZATION OF DRUG TREATMENT AS A MEANS OF ONCHOCERCIASIS CONTROL WITH PARTICULAR REFERENCE TO IVERMECTIN AND TO THE OCP AREA
ONCHOCERCIASIS CONTROL PROGRAMME IN WEST AFRICA

THE ROLE, IMPACT AND ORGANIZATION OF DRUG TREATMENT AS A MEANS OF ONCHOCERCIASIS CONTROL WITH PARTICULAR REFERENCE TO IVERMECTIN AND TO THE OCP AREA

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A. BACKGROUND AND GENERAL CONSIDERATIONS

1. The search for a drug

1.1 In the absence of an effective and convenient anti-onchocerciasis drug amenable to large-scale distribution, the basic technical approach of the Onchocerciasis Control Programme in West Africa (OCP) has so far consisted of controlling the vector in order to interrupt the transmission of the parasite. However, OCP is making considerable efforts through the Onchocerciasis Chemotherapy Project (OCT) to identify and develop medicaments of potential interest to the control of the disease.

2. The purposes and effects of drug treatment in the context of onchocerciasis control

2.1 The use of a drug in the control of onchocerciasis could serve two purposes: to treat patients suffering from the disease and to control transmission. Transmission-control by means of a drug would mean reducing/eliminating the production of microfilariae in the already infected part of the population (chemotherapy) and/or preventing larval stages of the parasite in previously non-infected persons from developing into reproductive adult worms (chemoprophylaxis); however, with the present limited knowledge of the two modes of action their respective contributions to the control of transmission will not be considered separately in this paper.

2.2 The use of a drug for the first purpose, i.e. the management of individual cases of onchocerciasis (case-treatment), aims at alleviating human suffering by easing symptoms of the disease, preventing its serious skin and ocular manifestations and, eventually, achieving complete cure. Although the emphasis here is on the treatment of individuals, the suppression/elimination of the microfilaria load will also contribute to transmission-control.

2.3 Given an ideal drug and perfect logistics, complete transmission-control and elimination of the *O. volvulus* reservoir should theoretically be possible without vector control. In practice, however, for some time to come (if ever) no drug is likely to conform with the requirements (100% effective, no side-effects, no exclusion criteria, etc.), and the demands for delivery systems and on resources could well exceed the national capacity. Anti-onchocerciasis drugs are therefore not likely to replace larviciding in the OCP area as a means of transmission-control.

2.4 It is expected that the effect of drugs used in the OCP area would be equally potent as regards the treatment and control of both the "blinding" ("savanna") and "non-blinding" ("forest") forms of onchocerciasis.

2.5 Whether the drug is a macrofilaricide or a microfilaricide, the ultimate effect should, in principle, be the same both in respect to transmission-control and to case-treatment. The difference will be one of application. One single treatment should suffice for the macrofilaricide (under ideal conditions) while a microfilaricide will need to be given at regular intervals (depending on the duration of its effect) until the reproductive female worms die out (12-15 years) (unless it also had a cumulative macrofilaricidal effect).
3. Registration

3.1 Phase III trials of ivermectin were started in 1985 and Merck, Sharpe & Dohme (MSD) intends to apply for registration based on a twelve-month follow-up of these trials. It is hoped that approval will be granted by July 1987. The application will probably be submitted to the French Drug Registration authorities which, in case of acceptance, should facilitate the approval of the drug for use by all those countries in Africa, America and Asia where onchocerciasis is endemic.

3.2 There may be a time-lapse of some months between registration and marketing.

4. Caveats and exclusion criteria

4.1 MSD is likely to put forward a number of caveats for the use of ivermectin, most of which might be issued as exclusion criteriae by WHO. At the present time the following population groups would probably be excluded from treatment:

- children below a certain age, say eight years.\(^1\)
- women of child-bearing age unless a pregnancy test, or history and absence of signs, show them not to be pregnant.
- women who are breastfeeding.\(^1\)
- persons with severe disease of the liver, kidney or central nervous system.
- persons living in an area exposed to epidemics of cerebro-spinal fever or human trypanosomiasis at the time of the proposed ivermectin treatment.\(^1\)

4.2 Furthermore, MSD will in all likelihood issue the following additional caveats:

- initially, ivermectin should be used only in the treatment of human onchocerciasis.
- the minimum interval between single doses should be six months although three-month intervals might eventually be permitted (see paragraph 5.2 below).

4.3 Also, the company will, no doubt, make available to the medical profession information regarding such pharmacodynamic aspects of ivermectin as the degree to which it is retained in the body with possible later release, its possible toxic manifestations, and the antidotes to be used if toxicity occurs.

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\(^1\)May subsequently be relaxed.
5. Dosage and formulation

5.1 The minimum effective single dose of ivermectin recommended by MSD is likely to be 150 mcg/kg, but scored tablets of 6 mg will be manufactured permitting easy dosage in the range of 50-200 mcg/kg.

5.2 The maximum interval between individual doses may vary according to the purpose of dispensing the drug. It would thus appear that one dose every six months might maintain adequate microfilarial suppression for most purposes (including transmission-control) although three to six month intervals could be necessary for case-treatment when there is a high risk of ocular onchocerciasis developing into blindness. However, an interval of three months must, for the time being, be regarded as the minimum compatible with safety. Ivermectin is known to persist in the body (especially in fat and certain other issues) for at least a month after a single dose, and it must be considered that there is an as yet unassessed risk of toxicity associated with the dosage given more frequently than once every three months.

6. Marketing and distribution control

6.1 It is likely that ivermectin will be supplied by MSD through WHO only for use in onchocerciasis-afflicted countries at a very reasonable or zero cost.

6.2 In order to avoid individuals receiving the drug, either inadvertently or deliberately, at shorter intervals than the minimum recommended (see paragraph 5.2 above) a fairly strict control must be kept on the delivery system and this in particular if multiple outlets are available (e.g. hospitals, health centres, OCP sectors/sub-sectors) to each of which an individual might apply for treatment in relatively quick succession.

C. POTENTIAL USE OF IVERMECTIN IN THE OCP AREA

7. General considerations

7.1 The main-characteristics of ivermectin which make it particularly amenable to use within the OCP area can be summarized as follows: it can be given orally in a single dose, repeatable probably every three to twelve months; it is highly effective as a microfilaricide, without serious side-effects; and thus suitable for large-scale distribution as and when required.

7.2 It is important to stress that ivermectin is effective against the forms of *O. volvulus* found in both savanna and forest areas in West Africa (and in Guatemala). It is reasonable to assume that it will act satisfactorily against all geographical forms of the parasite.

7.3 One limitation on the use of ivermectin would be that perhaps half of the female population will escape treatment if the above mentioned exclusion criteria (pregnant and lactating women as well as children below the age of eight) continue to apply. A rough assumption is that only 65% of the total infected population will be treatable.

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2See Annex 2 for recapitulation.
7.4 However, the reduction in the effect on transmission control resulting from exclusions would not attain 35%, as suggested in the preceding paragraph, if the findings of a study carried out in Cameroon rain-forest villages (main vector: S.squamosum) were valid also in the OCP area. According to this study 85% of transmission originated from persons between 11 and 40 years; up to age 20, males and females contributed equally to transmission but above 20, males contributed 1.5 times as much as females; and children aged 6-10 years were responsible for only about 6% of the total transmission. The application of these estimates to the situation in the OCP area would seem to indicate that the reduction in transmission control due to the exclusion of children, pregnant and lactating women from treatment, would be in the order of 20-25% rather than 35%.

7.5 An attempt is made in Annex 1 to estimate the numbers of persons who, if large-scale treatment with ivermectin were contemplated, would actually qualify for receiving the drug (estimates for 1987). At the same time, an analysis of these figures throws some interesting light on the cost-effectiveness of using ivermectin in various parts of the OCP area.

7.6 The calculations have been made separately for the original OCP area and for the three extension areas, viz Ivory Coast (1979), the Western Extension (1986/87) and the Southern Extension (1986/87) areas. Separate estimates are made in Annex 1 for the numbers of persons to be treated if a diagnostic survey preceded treatment of detected positives and if a blanket treatment of communities in the endemic areas were made without prior diagnostic surveys.

7.7 These estimates are referred to in the following when arriving at conclusions regarding the use of ivermectin. It should be stressed that many of the assumptions on which the calculations are based are open to discussion.

8. Use of ivermectin in the pre-Extension area (1985-boundaries)

8.1 Onchocerciasis has now been controlled in the major part of the original Programme area (00Z 01) to the extent that it is no longer a public health problem and that transmission of the parasite is virtually interrupted. However, there remains a reservoir of O. volvulus which, although greatly diminished, might still have the potential for becoming a source of renewed transmission. Further research is therefore required to determine the level of the parasite (microfilariae) load at which vector control may eventually cease. In the few residual areas where low-level transmission continues, the risk of developing ocular manifestations is probably insignificant (ATP below 300).

8.2 The situation in areas exposed to reinvasion of infective savanna blackflies remains unsatisfactory insofar as the downward trend of the community load of infection has been halted and the continuing exposure to new infections gives rise to onchocercal eye manifestations.

8.3 In those parts of the original OCP area where transmission is virtually interrupted and vector control is at the maintenance level (e.g. 00Z 01) there will be little, if any, use of ivermectin for the purpose of transmission control. Also the need for treatment of individual patients will be insignificant insofar as very few clinical cases remain after more than ten years of continuing vector control.

8.4 The principal use by the Programme of ivermectin within the original OCP area will therefore be the treatment (or prevention) of new cases that may occur due to reinvasion of infective blackflies or as a result of persistent localized failure in larvicidal control such as has occurred in a few small foci. Given that larviciding will extend to the OCP Extension areas over the next two or three years, the problem of reinvasion should become one of minor concern. However, should isolated instances of reinvasion of infective savanna blackflies (ATP above 300) ever occur, large-scale distribution would be instituted in exposed villages both for the purpose of transmission-control and case-treatment. Ivermectin could be used in a similar manner and with the same intentions in cases of resumption of transmission due to local failure of larviciding in a limited geographical area. In such places it would be used as a supplement to larviciding with the goal of reducing the microfilarial reservoir more rapidly than would otherwise occur.

8.5 For the sake of completeness, mention should be made of the possibility of ivermectin being utilised for transmission-control in circumscribed instances of unmanageable resistance to larvicides although such instances are unlikely to occur in the original OCP area.

8.6 The following consideration concerning cost-effectiveness of ivermectin treatment in the original OCP area supports the conclusions arrived at in paragraph 8.3 above. According to the estimates in paragraph 2 of Annex 1, if blanket treatment for the purpose of transmission-control were instituted, a total of more than four million people in the original OCP area would have to be given the drug in one year (1987) to reach the 338,000 persons still harbouring parasites. Ivermectin would thus be dispensed to 13 people to catch one lightly infected case, a cost-effectiveness ratio likely to decrease even further with time.

8.7 The conclusion to be drawn from these estimates would seem to be that ivermectin treatment in the original OCP area for the purpose of vector control would involve considerable extra expense without the expectation of any great additional benefit to that obtained by simply waiting for the elimination of the reservoir through natural death of parasites.

8.8 The treatment by ivermectin of patients suffering from the non-blinding form of onchocerciasis within forest and mixed forest/savanna areas, now excluded from control by OCP, would become the responsibility of the national health authorities, possibly with some technical advice from the Programme.

9. Use of ivermectin in the Extension areas

9.1 In paragraph 2.2 above it is suggested that the ideal drug dispensed under perfect conditions of logistics could by itself result in complete transmission-control achieved in the OCP area by larviciding as a sole means of control. However, as there is no complementarity in the action of the two methods (at least during the attack/consolidation phase) a choice imposes itself. Given, therefore, that vector control has proved itself to be capable of complete interruption of transmission, and insofar as the distribution of ivermectin will be encumbered by a number of technical and operational restrictions, larviciding will remain the preferred, and exclusive, method of transmission-control in the Extension areas during the attack/consolidation and beginning of the maintenance phase.
9.2 On the other hand, with a high morbidity level, reaching hyperendemic proportions in many parts of the Southern and Western Extension areas, there is a considerable potential for the use of ivermectin to alleviate the symptoms of onchocerciasis and prevent the further development of ocular manifestations in the large populations afflicted by the disease.

9.3 As and when the Extension areas move into the maintenance phase with a gradually diminishing community load of infection and greatly reduced risk of transmission, ivermectin will come to play the same role as that described in the preceding section in regard to the original OCP area, i.e. to control sporadic occurrences of localized O. volvulus transmission and to treat patients infected by the disease during such outbreaks (should they ever occur).

9.4 According to the calculations made in paragraph 6 of Annex 1, blanket treatment with ivermectin would (in 1987) cover a total population in the Extension areas of slightly more than three million in order to reach the one million requiring treatment. Three persons would therefore be given the drug to catch each infected case (often heavily infected). Blanket treatment might therefore be the most cost-effective approach to ensuring that all cases of onchocerciasis in high-risk areas are treated. However, further thought might be given to the economy of scale. It could thus be argued that once the initial "extra" efforts had been expended on case-finding, large-scale treatment limited to persons showing symptoms of the disease might be less expensive than conducting "indiscriminate" blanket treatment once or twice a year for a prolonged period.

9.5 As in the original Programme area, ivermectin could also be used on a large scale to control the non-blinding "forest" type of onchocerciasis within the Extension areas with the understanding that the role of OCP in this respect would be limited to the provision of technical advice.

D. ORGANIZATIONAL ASPECTS OF IVERMECTIN DISTRIBUTION

10. General considerations

10.1 When considering the relative cost-effectiveness of indiscriminate blanket treatment and of large-scale distribution confined to infected persons, as has been attempted in the two preceding sections, other factors than the number of persons to receive the drug should be taken into account, as for example, the likelihood that current diagnostic methods will miss a considerable population of lightly infected cases and the eventual pricing of ivermectin.

10.2 The need to avoid repetition of dosage leading to excess of the limits of safety (see paragraph 6.2 above) implies that records will have to be kept of all persons treated, a requirement which constitutes an important operational constraint on whichever delivery system is instituted.

10.3 The success of an ivermectin distribution programme (and indeed of any form of large-scale chemotherapy) will depend on the extent to which national health care systems are able to ensure the required population coverage and to continue doing so at the prescribed intervals during a prolonged period (12 years or more). Prerequisites for a community-based delivery system in any country would

4See Annex 2 for recapitulation.
appear to be political commitment and managerial competence; a reliable and
effective logistic and communication system; well-motivated, well-trained and
well-supported staff; the ability of the health system\(^5\) to penetrate into even
the most remote areas; and adequate funding. Proven ability to cope with other
public health programmes, such as EPI, in the recent past might serve as a good
yardstick by which to measure a country's potential ability for ivermectin
distribution.

10.4 Follow-up examinations should be carried out in a small number of indicator
villages with a view to determining the degree of thoroughness with which
ivermectin distribution is being carried out checking inter alia on the validity
of census figures, the issuing of tablets, and the immediate post-treatment
levels of ivermectin in plasma or urine in order to assess the assiduity of the
drug distributors. Such villages could also be used for assessing the success of
case-treatment in terms of decline of microfilarial densities in the skin and in
the eye. A particular aspect of follow-up would be the monitoring of the
possible development of resistance to ivermectin.

11. Organization of ivermectin distribution during period of OCP conducted
vector control operations

11.1 As a general principle ivermectin distribution schemes should be based on
and conducted by the existing national health care systems as part of the ongoing
disease control activities.

11.2 However, in the case of large-scale application of the drug for the purpose
of case-treatment in the Extension areas (see paragraph 9.2 above) the present
staffing and communication facilities of most of the national health care systems
will probably not enable them to cope on their own with this additional workload.
Insofar, therefore, as OCP will be conducting attack/consolidation operations in
the two Extension areas while large-scale treatment with ivermectin is underway,
the OCP entomological surveillance network could very well be "mobilized" to aid
nationally directed drug distribution. Lax periods of the dry season when the
entomological situation is comparatively quiet would be particularly convenient.
The involvement of the Programme in mass case-treatment would seem perfectly
justified even if OCP's main concern lies in the field of transmission -control.
An added reason for making use of OCP staff in such large-scale distribution
programmes would be, at least in the Western Extension area, that all local
personnel, although assigned temporarily to the Programme, remain on the payroll
of the governments concerned.

11.3 An attempt is made in Annex 3 to obtain an idea about manpower requirements
for the Western Extension area (as an example) if blanket treatment were applied
twice a year for the purpose of treating all infected cases in the area.
According to this estimation, 45 teams (135 technicians, 45 drivers) would be
needed as compared with 400 national staff assigned to OCP in that area for
entomological surveillance alone.

11.4 An advantage of instituting ivermectin distribution at an early stage of
operations (attack/consolidation phase) would be that the national health care
systems became experienced in the management of mass application of the drug.
They would thus be prepared for handling local instances of renewed transmission
by means of drug control during the maintenance phase after the Programme has
moved out of the area (see section 12 below).

\(^5\)Possibly aided by other socioeconomic sectors.
11.5 During the first part of the maintenance phase in the Extension areas when OCP carries on with vector control as required, large-scale application of ivermectin for case-treatment purposes will continue although on a gradually reducing scale insofar as the original risk of repeated *O. volvulus* infections giving rise to serious ocular manifestations has been removed by vector control and the adult female worms begin to die out. Several modifications could then be made to the distribution scheme, including giving the drug once yearly instead of twice; concentrating on originally hyperendemic communities, and, possibly, limiting the treatment to persons who have been identified during previous treatment rounds as patients actually suffering from onchocerciasis, according to a set of easily applied signs and symptoms. The number of distribution teams would therefore be gradually reduced and by the time OCP vector control ceases in a given O02 there should be little, if any, need for case-treatment to be handled by special teams.

11.6 Special operational arrangements might be required for the coordination of large-scale OCP supported case-treatment programmes in savanna areas and those conducted by the national health authorities in neighbouring/overlapping forest zones for the control of the non-blinding form of the disease.

12. **Organization of ivermectin distribution during the post-OCP maintenance/surveillance period: Devolution and ivermectin**

12.1 Devolution has until recently been seen as a process of transfer of OCP operations (including vector control) to the Participating Countries, although at a reduced scale. Recently, however, it has become clear that devolution in that sense is an outdated concept; at the time the Programme "hands over" there will no longer be a need for vector control (onchocerciasis prevalence being at a level at which transmission is excluded). What will then be required is rather "nationally directed, integrated surveillance and control" of the disease.

12.2 The challenge facing the national health authorities at that stage will therefore be twofold: to ensure that new cases of onchocerciasis which may occur are actually detected (as any other endemic disease under epidemiological surveillance) and that appropriate action is taken for their control. This control will rely on the application of community-wide drug treatment of the populations among whom the new cases have appeared and in which recrudescence of transmission (local breeding) is suspected.

12.3 The gradual assumption by Participating Countries of this the final stage of onchocerciasis surveillance and control will follow the same pattern in the original and in the Extension areas, the former commencing the process within a comparatively near future and the latter in about eight to ten years.

12.4 It is expected that both the surveillance and the control of onchocerciasis will be integrated within the existing (and possibly reinforced) health care systems. Insofar as the use of the drug is concerned, ivermectin will serve both purposes: transmission-control, should new cases occur due to local breeding of savanna blackflies, and case-treatment of the patients thus contaminated. Another group of beneficiaries would be the originally infected populations in the Extension areas who have been treated since the start of attack operations; at the time of cessation of OCP operations in a given O02, this group will have been reduced considerably in size and should no longer require a special set-up for its treatment (see paragraph 11.5 above).
12.5 Although it is anticipated that community-wide application of ivermectin for the control of circumscribed retransmission would normally be handled by the existing local health care system, instances might occur when reinforcement could be required either from other parts of the health services or by recruiting additional personnel on a temporary basis. Such personnel would work under the instructions and control of the health services.

12.6 Again, individual national health authorities would decide on the extent to which ivermectin will be utilized for the control of "forest onchocerciasis" and could call upon OCP, and possibly WHO, for technical recommendations.

E. POTENTIAL USE OF SERODIAGNOSIS

13. General considerations

13.1 The Programme is strengthening its research in the field of serodiagnosis of onchocercal infections. The availability of a sensitive, specific and easily handled immuno-diagnostic test, capable of detecting recent infections (and possibly distinguishing between savanna and forest type), would help to ensure that newly infected patients could be detected and treated at an early stage of the disease, i.e. before microfilariae in the skin become a source of transmission. Also, a test fulfilling the above criteria would make the detection of instances of circumscribed transmission in otherwise transmission-freed zones easier. This would facilitate corrective action (transmission-control through drug distribution) and thereby eliminate the risk of further spread.

13.2 In this connection it is worth stressing that newly infected persons are not very likely to constitute a "hidden" source of infection during the prepatent period of the disease (from 1 to 3 dermal penetration until the onset of cutaneous manifestations) as blackfly cannot ingest microfilariae before they appear in the skin and subcutis and where they may give rise to itching. The first microfilariae are usually detectable in skin-snips only after, say, nine months to three years following penetration by the larvae. (N.B.: microfilariae may, however, be present in the skin and transmissible without positive skin-snips or symptoms).

13.3 Failing the development of a sensitive immunodiagnostic test suitable for field use, it may be necessary to consider using the Mazzotti test, either generalized or as a patch test, to detect microfilariae at a very early stage after their arrival in the skin.

14. Use of an immunodiagnostic test

14.1 Should an operational immunodiagnostic test be found, case-treatment might be "individualized" rather than based on large-scale application and, as mentioned above, transmission-control instituted at an early date.

14.2 However, the cost of applying and reading the test on a large-scale selective population basis would be quite high, in particular if "detection rounds" were to be made every six to twelve months.
F. DISTRIBUTION OF IVERMECTIN AND TECHNICAL COOPERATION

15. Support to the strengthening of health care delivery systems

15.1 The organization and management of drug-distribution programmes in the Participating Countries will put considerable strain on the national health care systems, which are already operating under serious constraints as regards manpower and material resources. It is therefore encouraging that several representatives of the donor community at recent sessions of the Joint Programme Committee have expressed readiness to support countries in the Programme area in respect to their assuming operational responsibility for post-OCP surveillance and control of onchocerciasis.

15.2 The strengthening of the health care systems to be able inter-alia to deal with large-scale distribution of ivermectin must continue to be given priority attention. WHO, through its regional office for Africa, is reinforcing its technical cooperation with its Members through a process of decentralization of authority and operational responsibility. Particular emphasis is placed upon the development of primary health care systems which in West African countries will play an essential role in the conduct of future schemes for the distribution of ivermectin.

15.3 Furthermore, WHO has a constitutional role to play in ensuring that external support to health development is provided in a coordinated manner and according to policies and priorities commonly agreed upon. The bilateral donor agencies which have already indicated willingness at JPC sessions to assist Participating Countries in strengthening their health care delivery systems should be encouraged to consult with WHO/APRO in order to ensure that all efforts to enhance these systems are well coordinated.

16. Support to procurement of ivermectin

16.1 Another field in which international solidarity will be of importance is that of supply of ivermectin. Although it is expected that the drug will be distributed at almost no cost, large quantities could be required, in particular for case-treatment in the Extension areas, and the total cost of distribution might very well be beyond the reach of some of the countries concerned. Several organizations and agencies, governmental and non-governmental, particularly interested in the prevention of blindness, might be prepared to help in this respect. WHO/APRO and OCP could make an important contribution by organizing bulk-supply of the drug and possibly by setting up a revolving or special fund.

G. FURTHER INVESTIGATIONS AND OPERATIONAL RESEARCH CONCERNING THE USE AND DISTRIBUTION OF IVERMECTIN IN OCP AND OTHER ONCHOCERCIASIS-INFESTED AREAS

17. Issues and studies of direct relevance to the use of ivermectin

17.1 The following issues will need to be addressed:
   a. mode of action of ivermectin on Onchocerca at the biochemical and molecular levels
b. degree and duration of effect of ivermectin in reducing the number of *O. volvulus* L3 developing in *Simulium* fed on microfilarial carriers in different environments and vectors

c. histology of skin in onchocercal patients after ivermectin treatment, together with other immunological and biochemical investigations to determine why the Mazotti reaction is so much less intense than with DEC

d. effect of multiple doses of ivermectin, at different intervals, on reproduction of *Onchocerca* worms (*O. volvulus* in man and *O. gibsoni* in cattle) and on possible macrofilaricidal activity as well as estimates of concentration and persistence of the drug in adult worms and nodules

e. epidemiological studies on effect of community-wide ivermectin treatment on microfilarial reservoir and on the amount of transmission of *O. volvulus* (measured by ATP) occurring in and around isolated communities in endemic onchocerciasis areas without satisfactory vector control

f. therapeutic potential of ivermectin followed by a course of low-dose suramin (or any other macrofilaricidal developed in future) especially as regards prevention of development of eye lesions; curing acute pruritic skin lesions; and alteration of toxic manifestations associated with suramin

g. optimal interval of dosing to prevent development of eye lesions and to cure/prevent acute pruritic dermal lesions and "sowda"

h. the safety of ivermectin in pregnant women, lactating women and children below the age of eight years

i. tolerance to ivermectin in patients receiving antimalarials (e.g. chloroquine, quinine and pyrimethamine/sulphonamide) or other drugs like benzodiazepines

j. possible caution re. use of ivermectin in areas where *Loa loa* and *O. volvulus* co-exist as ivermectin treatment could, theoretically, cause severe reactions in brain or retina due to sudden death of large numbers of *L. loa* microfilariae

k. collection and analysis of data on possible adverse reactions following the marketing of ivermectin within the OCP area

l. close watch for development of resistance to ivermectin even if this unlikely; however, should resistance occur it would probably spread very slowly due to long generation turnover time in *O. volvulus* and absence of microfilaria multiplication in the vector; resistance would be likely to spread more rapidly in areas without vector control, while spread would be almost nil as long as adequate vector control is maintained.

17.2 Although the more basic research issues would seem to be the concern of MSD, OCP will have to be involved in studies relating to some of the epidemiological/operational research subjects listed above.
18. Issues and studies of direct relevance to the distribution of ivermectin

18.1 In connection with large-scale application of ivermectin, OCP could usefully undertake the following studies:

a. an estimation of the cost of diagnostic surveys of *O. volvulus* immediately followed by ivermectin treatment of all persons found positive and not subject to exclusion criteria (on a country-by-country basis)

b. an estimation of the cost of instituting blanket treatment without a pre-treatment diagnostic survey, but observing the exclusion criteria (on a country-by-country basis)

c. prediction as to the level of community load of infection below which no transmission would occur if savanna blackfly were allowed to re-enter the area

d. predictions as to the possible effects of ivermectin treatment on the human microfilarial reservoir in different parts of the OCP area and on the amount of transmission that would result if the *S. damnosum* s.l. population were allowed to build up again (on the basis of pre-treatment diagnostic survey and on the basis of blanket treatment; consideration given to the effect of applying exclusion criteria)

e. R & D field studies to identify various organizational and managerial approaches to large-scale application of ivermectin for the purposes of transmission-control and case-treatment (on a country-by-country basis) and cost/benefit studies area-wise

f. R & D studies to identify the gradual decline in workload associated with large-scale case-treatment in Extension areas following effective vector control and the dying out of female worm.

H. POTENTIAL USE OF IVERMECTIN IN ONCHOCERCIASIS-INFESTED AREAS WITHOUT OCP-LIKE CONTROL PROGRAMMES

19.1 As in the OCP area, ivermectin could serve the dual purpose of case-treatment and transmission-control in countries where onchocerciasis is endemic and where no systematic, complete-coverage vector control programme has been instituted.

19.2 To secure an epidemiologically significant effect on transmission within a given onchocerciasis-infested area, ivermectin would need to be given at regular intervals to all infected persons. If the area in question extends to the limits of transmission of the disease so that there is no risk of infective blackflies entering the area from outside sources, ivermectin distribution over a period of 12-15 years should, theoretically, result in the human *O. volvulus* reservoir dying out and the disease being eliminated. However, under practical field conditions with probable incomplete coverage at irregular intervals and the need to apply the exclusion criteria, the effect of large-scale ivermectin distribution on transmission may only be palliative with the prospect of an indefinite continuation.
19.3 Obviously, the situation in a more confined endemic area exposed to reinvasion of infective blackfly would be even more unsatisfactory, insofar as any temporary ivermectin-induced reduction in transmission of the parasite would cancel out once drug distribution ceased and infective blackfly from the outside joined with those still active in the area to bring the human O. volvulus reservoir back to its pre-distribution level. However, there would be a beneficial effect in terms of preventing infected persons from developing serious eye-lesions.

19.4 On the other hand, if large-scale distribution of ivermectin is likely to have only a temporary effect on transmission, the use of the drug for the purpose of case-treatment (preventing serious skin and eye manifestations) could be of considerable benefit to those infected by the disease for as long as the treatment continued, even if the risk of re-infection would persist.

J. POTENTIAL USE AND EFFECT OF A MACROFILARICIDE

20.1 The availability of the long-acting microfilaricide, ivermectin, by no means precludes the pressing need for a non-toxic macrofilaricidal drug, suitable for large-scale use. It may be that one of the new Ciba-Geigy compounds, CGP 6140 or CGP 20376, would fill this role within the foreseeable future, but meanwhile research for others must be intensified.

20.2 Large-scale distribution of a macrofilaricide aiming at the populations already infected by, or exposed to, onchocerciasis would greatly enhance the effect of vector control and reduce its duration. Furthermore, in areas without systematic vector control, blanket treatment by a macrofilaricide in combination with ivermectin, might conceivably reduce the human reservoir of O. volvulus in all its forms to a non-transmissible level within a comparatively short time.

20.3 Finally, as with ivermectin, a macrofilaricide would be used also for the control, and possibly elimination, of the non-blinding ("forest") form of onchocerciasis.
Estimation of the number of beneficiaries of ivermectin treatment in the OCP area (1987)

1. Table I below refers to the original OCP area. For each of the seven countries it gives (a) the estimated number of persons infected with O. volvulus in 1974; (b) the numbers probably still infected in 1987 (taking these to be 25% of the 1974 figures); (c) the number of those in (b) able to take treatment with ivermectin (taken as 80% of those in (b), assuming that exclusion criteria will apply only to pregnant/lactating women and those with severe disease of liver, kidney, etc. - not to children under 8, who will no longer be part of the infected population); (d) the estimated total population over 10 years old living in erstwhile endemic areas in 1987 (taken as 110% of the OCP Planops figures for 1984 less 20% for those under 10); and (e) the number of those in (d) who would be able to take ivermectin treatment (80% of those in (d)).

2. For the original OCP area 423,000 (probably lightly) infected persons would require treatment in 1987, and 338,000 would be able to take ivermectin. If blanket treatment was given to all those over 10 years of age who could take ivermectin and will then be living in the erstwhile endemic areas it would be necessary to treat nearly 13 persons in order to catch each lightly infected case, and the cost-effectiveness of treatment is likely to continue decreasing even more rapidly with each succeeding year.

### Table I

<table>
<thead>
<tr>
<th>Country</th>
<th>(a) Number of persons infected with O. v. in 1974</th>
<th>(b) Number of persons infected with O. v. in 1987</th>
<th>(c) Number able to take ivermectin</th>
<th>(d) Population over age of 10 in erstwhile endemic areas</th>
<th>(e) Number of those in (d) able to take treatment with ivermectin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benin</td>
<td>120,000</td>
<td>30,000</td>
<td>24,000</td>
<td>190,000</td>
<td>152,000</td>
</tr>
<tr>
<td>Burkina Faso</td>
<td>640,000</td>
<td>160,000</td>
<td>128,000</td>
<td>2,640,000</td>
<td>2,112,000</td>
</tr>
<tr>
<td>Ghana</td>
<td>310,000</td>
<td>78,000</td>
<td>62,000</td>
<td>998,000</td>
<td>798,000</td>
</tr>
<tr>
<td>Ivory Coast</td>
<td>200,000</td>
<td>50,000</td>
<td>40,000</td>
<td>620,000</td>
<td>496,000</td>
</tr>
<tr>
<td>Mali</td>
<td>320,000</td>
<td>80,000</td>
<td>64,000</td>
<td>704,000</td>
<td>563,000</td>
</tr>
<tr>
<td>Niger</td>
<td>20,000</td>
<td>5,000</td>
<td>4,000</td>
<td>44,000</td>
<td>35,000</td>
</tr>
<tr>
<td>Togo</td>
<td>80,000</td>
<td>20,000</td>
<td>16,000</td>
<td>192,000</td>
<td>154,000</td>
</tr>
<tr>
<td>Total</td>
<td>1,690,000</td>
<td>423,000</td>
<td>338,000</td>
<td>5,388,000</td>
<td>4,310,000</td>
</tr>
</tbody>
</table>

(a) Source-PAG report 1974
(b) At 25% of 1974 figures
(c) At 80% of figure in column (b) (i.e. assuming 20% exclusions from pregnant/lactating women, etc.)
(d) OCP planops estimate for 1984 with 3.5% annual growth = 110% of 1984, less 20% for those under 10 years old
(e) 80% of (d)

All figures rounded to nearest 1000

1 This ratio could of course be improved if blanket treatment were to be applied only to those communities with the highest original (1974) prevalence and intensity levels.
3. Table II relates to the extension into southern Ivory Coast which took place in 1979. The same assumptions have been made as for Table I except that the 1987 figures for the number of persons infected have been calculated at 50% of the 1979 figures. In 1987 there will be 255 000 infected persons requiring treatment and 204 000 able to take it. Blanket treatment in the endemic areas would involve treating 1 389 000 persons, i.e. 6.8 persons would have to be treated in order to catch each infected case.

4. However it should be noted that the degree of larvicidal control achieved in the southern Ivory Coast has been less than completely satisfactory so that the total number of infected persons in 1987 may well be considerably greater than is shown in Table II. Furthermore, most of the onchocerciasis in this area is of the forest form, whose control is essentially a national responsibility.

Table II
EXTENSION IVORY COAST (1979)

<table>
<thead>
<tr>
<th>Country</th>
<th>(a) Number of persons infected with O.v</th>
<th>(b) Number of persons infected with O.v</th>
<th>(c) Number able to take treatment</th>
<th>(d) Population over 6 years of age living in erstwhile endemic areas</th>
<th>(e) Number of those in (d) able to take treatment with ivermectin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ivory Coast</td>
<td>510 000</td>
<td>255 000</td>
<td>204 000</td>
<td>1 738 000</td>
<td>1 390 000</td>
</tr>
</tbody>
</table>

(a) Source PAG
(b) At 50% of 1979 figures
(c) At 80% of 2
(d) 110% of OCP Planops 1984 less 12% for those under 6 years old

5. Tables III and IV on the following page refer to the Western and Southern Extension areas respectively, where larviciding is due to start in 1986/87. For each country are given (a) the estimated number of persons infected with *O. volvulus* in 1987 (based on the Senegambia report figures + 3%); (b) the number of these able to take treatment with ivermectin (taken as 65% of those in (a), i.e. excluding children under 8, pregnant and lactating women, etc.); (c) the population that will be living in the endemic areas in 1987 (based on the Senegambia report figures plus 3%); and (d) the numbers of those in (c) who will be able to take ivermectin (again 65% of (c)).

6. For the Western and Southern Extension areas respectively 1 082 000 and 525 000 persons require treatment with ivermectin in 1987 and 703 000 and 342 000 would be able to take the drug. If blanket treatment were to be given to
all those living in the endemic areas it would be necessary to treat 2,277,000 and 825,000 persons respectively. In other words blanket treatment would involve treating 3.2 persons in the western extension and 2.4 persons in the southern extension in order to catch each infected case (many of which would be heavily infected).

### Table III
**EXTENSION AREA (WEST) 1986/87**

<table>
<thead>
<tr>
<th>Country</th>
<th>(a) Number of persons infect with O.v in 1987</th>
<th>(b) Number able to take treatment with ivermectin</th>
<th>(c) Population living in endemic areas</th>
<th>(d) Number of those in (c) able to take treatment with ivermectin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guinea</td>
<td>577,000</td>
<td>375,000</td>
<td>2,060,000</td>
<td>1,339,000</td>
</tr>
<tr>
<td>Guinea Bissau</td>
<td>31,000</td>
<td>20,000</td>
<td>103,000</td>
<td>67,000</td>
</tr>
<tr>
<td>Mali</td>
<td>288,000</td>
<td>187,000</td>
<td>721,000</td>
<td>469,000</td>
</tr>
<tr>
<td>Senegal</td>
<td>52,000</td>
<td>34,000</td>
<td>206,000</td>
<td>134,000</td>
</tr>
<tr>
<td>Sierra Leone</td>
<td>134,000</td>
<td>87,000</td>
<td>412,000</td>
<td>268,000</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td><strong>1,082,000</strong></td>
<td><strong>703,000</strong></td>
<td><strong>3,502,000</strong></td>
<td><strong>2,277,000</strong></td>
</tr>
</tbody>
</table>

(a) Senegambia report + 3%
(b) 65% of 1 (i.e. excluding children under 8 years old; pregnant/lactating women, etc.)
(c) Senegambia report + 3%
(d) 65% of 3

### Table IV
**EXTENSION AREA (SOUTH) 1986/87**

<table>
<thead>
<tr>
<th>Country</th>
<th>(a) Number of persons infect with O.v in 1987</th>
<th>(b) Number able to take treatment with ivermectin</th>
<th>(c) Population living in endemic areas</th>
<th>(d) Number of those in (c) able to take treatment with ivermectin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benin</td>
<td>278,000</td>
<td>181,000</td>
<td>500,000</td>
<td>325,000</td>
</tr>
<tr>
<td>Ghana</td>
<td>103,000</td>
<td>67,000</td>
<td>377,000</td>
<td>245,000</td>
</tr>
<tr>
<td>Togo</td>
<td>144,000</td>
<td>94,000</td>
<td>393,000</td>
<td>255,000</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td><strong>525,000</strong></td>
<td><strong>342,000</strong></td>
<td><strong>1,270,000</strong></td>
<td><strong>825,000</strong></td>
</tr>
</tbody>
</table>

(a) Senegambia report + 3%
(b) 65% of 1
(c) Senegambia report + 3%
(d) 65% of 3
Recapitulation of the potential use of ivermectin and of the organization of its distribution within the OCP area

<table>
<thead>
<tr>
<th>Operational phase:</th>
<th>Purpose</th>
<th>Transmission-control</th>
<th>Case-treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>binding form</td>
</tr>
<tr>
<td>Attack/consolidation (Extension areas)</td>
<td></td>
<td>-no scope for ivermectin; transmission control by OCP larviciding</td>
<td>-large-scale ivermectin distribution</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>national with OCP teams</td>
</tr>
<tr>
<td>Maintenance, OCP</td>
<td></td>
<td>-no scope (as above)</td>
<td>-continuation of ivermectin distribution in Extension areas</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>national with OCP teams (fewer)</td>
</tr>
<tr>
<td>Maintenance, national</td>
<td></td>
<td>-use of ivermectin for control of local outbreaks of transmission</td>
<td>-as above and treatment of &quot;outbreak&quot; cases</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>national (PHC)</td>
</tr>
</tbody>
</table>
Estimation of manpower requirements
for large-scale case-treatment in Western Extension area

1. One team of three technicians and one driver should be able to register and treat 540, say, 500 persons per day (8 hours) counting on two minutes per person and two hours transport.

2. If the target population is to be treated once a year during two rounds of two months each, 50,000 persons in all would be "covered" by one team in one year.

3. 2,277,000 persons would be included in the programme of blanket treatment in the Western Extension area\(^1\) thus requiring the services of, say, 45 teams (135 technicians and 45 drivers) during four months of the year.

\(^1\)See Annex 1, Table III.