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SUMMARY OF  
FINAL EVALUATION OF THE  
POPULATION COUNCIL ACTIVITIES  
CONDUCTED UNDER COOPERATIVE AGREEMENT  
DPE-3005-A-00-3003

Based on a Report

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covering the period  
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TABLE OF CONTENT

GLOSSARY . . . . .	iii
NOTE . . . . .	iv
EXECUTIVE SUMMARY . . . . .	v
1. INTRODUCTION . . . . .	1
2. CONTRACEPTIVE DEVELOPMENT PORTFOLIO . . . . .	2
2.1 The Portfolio . . . . .	2
2.1.1 Summary . . . . .	2
2.1.2 Subdermal Implants . . . . .	2
2.1.3 Levonorgestrel IUD (LNG IUD) . . . . .	5
2.1.4 Contraceptive Vaginal Rings . . . . .	6
2.1.5 Barrier Methods . . . . .	7
2.1.6 Luteinizing Hormone Releasing Hormone (LHRH) Analogues . . . . .	7
2.1.7 Inhibin . . . . .	9
2.1.8 Other New Leads . . . . .	10
2.1.9 Summary of Recommendations for Contraceptive Development . . . . .	11
2.2 Staffing and Funding . . . . .	12
2.2.1 Staffing . . . . .	12
2.2.2 Funding . . . . .	13
2.3 Conclusions and Recommendations . . . . .	13
3. CONTRACEPTIVE INTRODUCTION . . . . .	15
3.1 Overall . . . . .	15
3.2 NORPLANT <sup>R</sup> . . . . .	15
3.2.1 Progress to Date . . . . .	15
3.2.2 Introductory Activities . . . . .	16
3.2.3 Constraints . . . . .	17
3.3 Copper T380A IUD . . . . .	18
4. FAMILY PLANNING PROGRAM COMPONENT . . . . .	19
4.1 Overview . . . . .	19
4.2 Programs by Region . . . . .	19
4.2.1 Latin America . . . . .	19
4.2.2 Asia . . . . .	20
4.2.3 Africa . . . . .	20

4.3	Management . . . . .	22
4.4	Assessment of Value of Family Planning Component to A.I.D.. . . . .	22
5.	PRINCIPAL CONCLUSIONS AND RECOMMENDATIONS . . . . .	25
5.1	Conclusions . . . . .	25
5.2	Recommendations . . . . .	25

GLOSSARY

AVSC	Association for Voluntary Surgical Contraception
FDA	Food and Drug Administration
FHI	Family Health International
FPIA	Family Planning International Assistance
GnSIF	Gonadotropin Surge Inhibiting Factor
ICCR	International Committee for Contraception Research
IPPF	International Planned Parenthood Federation
IPPF/WHR	International Planned Parenthood Federation/ Western Hemisphere Region
JHPIEGO	Johns Hopkins Program for International Education in Gynecology and Obstetrics
IP	International Programs
LHRH	Luteinizing Hormone Releasing Hormone
LNG	Levonorgestrel
NDA	New Drug Application
PIACT	Program for the Introduction and Application of Contraceptive Technology
R&D	Research and Development
STD	Sexually Transmitted Disease
UNFPA	United Nations Fund for Population Activities

NOTE

This summary report is based on an evaluation report by Michael J. K. Harper, Terrence W. Jezowski, Michael E. McClure, and J. Joseph Speidel. The full report can be obtained from the Population Technical Assistance Project of the International Science and Technology Institute, Inc.

## EXECUTIVE SUMMARY

A.I.D.'s support to the Population Council for contraceptive development, contraceptive introduction, and family planning program development has been extremely productive and worthwhile.

The Council has been one of the most successful public sector programs in the contraceptive development field and has introduced more new methods to the marketplace than any other program. In addition to NORPLANT<sup>R</sup> and the Copper T380A IUD, which are now in the introduction stage, the Population Council is developing several promising new products, including NORPLANT<sup>R</sup>-2 rods and the levonorgestrel (LNG) IUD. Other exciting leads being developed include second generation implants containing the steroids ST-1435 and 3-Ketodesogestrel and three different vaginal rings. A.I.D. support has been critical in ensuring continued progress by the program and has been a most successful investment as judged by both actual and potential returns. The quality of the research performed, both basic and applied, has been exceptional.

The major concerns involve the sufficiency of staffing in certain key areas of the contraceptive development process, e.g., dosage formulation, toxicology, regulatory affairs, clinical trial coordination, and monitoring. Some of the delays in registration of NORPLANT<sup>R</sup> in the U.S. can be attributed to this lack of manpower. If a number of contraceptive development tasks had to be carried out simultaneously, such as writing and compiling two or three NDAs, funds and staff would be a serious constraint and cause delays.

With respect to introduction activities for NORPLANT<sup>R</sup> and the Copper T380A, the Population Council has performed in an impressive manner. Progress has been slower for NORPLANT<sup>R</sup> than for the Copper T380A IUD, mostly because the new IUD has received FDA approval and can therefore be purchased by A.I.D. In the absence of FDA approval for NORPLANT<sup>R</sup>, the Council has correctly proceeded with caution and thoroughness to ensure that no mistakes occur that might set back the program. Another constraint has been lack of sufficient numbers of field staff.

The family planning program includes operations research, technical assistance, exploration of new programs, and production of information and educational materials. Following its considerable involvement in Asia and Latin America, the Council is now focusing primarily on Africa. Here, A.I.D. support has been crucial to the development, expansion and maturation of the Council's overall sub-Saharan Africa program. The Council's efforts in this sphere have also been responsive to A.I.D.'s own changing priorities over the years.

The major conclusion is that the work of the Council deserves continued and expanded support, with three major recommendations on how the program might be strengthened in the near future.

1) A.I.D. funding should be increased in a stepwise fashion over the next few years by about 50 percent over the current level of funding.

2) Additional staff should be recruited in several key areas related to product development, registration, and clinical trials to reduce the time to market for products now in the development pipeline.

3) The Population Council should develop a long-range plan specifying its view of the optimal size of the organization and optimal accommodation for such an organization (funding considerations aside). Such a plan could prove a useful management tool for solicitation of new funding.

Other principal recommendations include the following:

4) A.I.D. should continue its policy of line-item funding for the key major activities being supported such as NORPLANT<sup>R</sup>, NORPLANT<sup>R</sup>-2, levonorgestrel IUD, and vaginal ring studies. For flexibility and easier administration, however, a certain percentage (about 10 percent) of the total contraceptive development budget should be allocated for probing studies, and the Population Council should be allowed to decide how to allocate funds among them.

5) A.I.D. should increase funding for the contraceptive introduction program to permit recruitment of additional field staff, particularly one or two persons for Africa.

6) The Council should work closely with Leiras to ensure that each country's product registration activities for NORPLANT<sup>R</sup> go forward expeditiously.

7) The Council should seek greater involvement in their contraceptive introduction activities of major service delivery programs, donors that support such programs, and technical assistance agencies.

8) A.I.D. should maintain the capability to take advantage of the Population Council's field experience and expertise by continuing to support the family planning program component of the cooperative agreement.

## 1. INTRODUCTION

## 1. INTRODUCTION

This evaluation covers work carried out by the Population Council under an A.I.D. five-year \$23,536,140 cooperative agreement, DPE-3005-A-00-3003, scheduled for completion in July 1988. The evaluation focuses primarily on the Council's work in developing new contraceptive methods, carried out by its Center for Biomedical Research, together with its efforts to support systematic introduction of the contraceptives it has developed, carried out by its International Programs (IP) Division. Together, these programs account for about 85 percent of the funds allocated under the cooperative agreement. The evaluation also covers the activities in family planning design, implementation, evaluation, and dissemination managed by the IP Division, which constitute the other 15 percent of the program.

This is the second recent evaluation of the Council's contraceptive development program. The first, in 1983, concluded that the Population Council's program, with two products very near introduction, was one of the most successful programs in the contraceptive research and development (R & D) field. The Council has generally carried out the major recommendations contained in the first evaluation as follows:

1) More use has been made of consultants to the International Committee for Contraception Research (ICCR), whose members carry out most of the Council's clinical trials and perform development work in their own laboratories. Further expansion of the Committee's membership, however, is recommended as a means to assist the work of the Contraceptive Introduction Group.

2) The Population Council has done an excellent job in involving private industry in the contraceptive development process, having developed agreements with 10 companies.

3) The Council has strengthened its ability to carry out toxicology and quality assurance programs, areas needing strengthening as the development of contraceptives has proceeded.

4) On the other hand, the recommendation that assistance be provided to the staff member primarily responsible for writing New Drug Applications (NDA) for the Food and Drug Administration (FDA) was not implemented. This failure was viewed to be in part responsible for a three-year delay in the filing for an NDA for NORPLANT<sup>R</sup>.

## 2. CONTRACEPTIVE DEVELOPMENT PORTFOLIO

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### 2.1 The Portfolio

#### 2.1.1 Summary

The exceptionally high quality of the Population Council's work in contraceptive development continues to be evident. Historically, the Council has introduced more new methods to the marketplace than any other program. During the period being evaluated, two products--NORPLANT<sup>R</sup> and the Copper T380A IUD (see Chapter 3)--were in the Introduction phase.

Contraceptive development is an extremely long-term process. Therefore, most of the A.I.D.-supported leads under development during this evaluation period were under development at the time of the first evaluation: subdermal implants including NORPLANT<sup>R</sup> and NORPLANT<sup>R</sup>-2 and some second generation implants; the LNG IUD; contraceptive vaginal rings; and luteinizing hormone releasing hormone (LHRH) analogs. A.I.D. has also supported other newer avenues of exploration including the gonadal proteins inhibin and gonadotropin surge inhibiting factor (GnSIF). In addition to its A.I.D.-supported activities, the Population Council has also undertaken research with non-A.I.D. funds on barrier methods, an anti-LHRH vaccine, and an antisperm vaccine.

The most promising products still in the development stage were found to be the NORPLANT<sup>R</sup>-2 and the levonorgestrel (LNG) IUD. Other exciting leads being developed include second-generation implants containing the steroids ST-1435 and 3-keto-desogestrel and three different vaginal rings.

#### 2.1.2 Subdermal Implants

The subdermal implant method entails introduction of a progestin in small tubes beneath the skin. The progestin diffuses out slowly to provide contraceptive effectiveness for as long as five years. The method provides long-term contraceptive action without requiring attention, except for the initial placement and eventual removal. The use of only a progestin in the implant avoids many of the more serious side effects that can be associated with estrogens as they are used in the combination pill.

The Council is involved in three major types of products: NORPLANT<sup>R</sup>, composed of six subdermal capsules; NORPLANT<sup>R</sup>-2, composed of two subdermal rods; and several types of second-generation implants, each type composed of a single subdermal rod.

2.1.2.1 NORPLANT<sup>R</sup>. NORPLANT<sup>R</sup> releases levonorgestrel (a synthetic hormone of the progestin family) through six capsules inserted beneath the skin of the upper arm. The system is effective for at least five years. Its introduction in family planning programs has advanced over the past four years and pre-introduction studies continue to show the low pregnancy and high continuation rates found in earlier clinical trials. NORPLANT<sup>R</sup> capsules are now approved for commercial distribution in 12 countries, and it is expected that an NDA will be submitted to the FDA by June 1988.

Safety studies continue, with no negative findings with regard to cholesterol levels, serum chemistry, adrenocortical function, or endometrial cancer. Post-marketing surveillance studies are being conducted in collaboration with WHO and Family Health International to ensure no unexpected long-term side effects.

A problem that has become apparent recently is that pregnancy rates are related to the weight of the user, and this effect is most prominent in later years of use (years 3-5) and in women weighing more than 70 Kg. There are some data indicating that changing the tubing of the capsule may correct the problem, and further research will be conducted to address this issue.

There has been a major delay in completing the NDA filing with the FDA, first anticipated for 1985 and now not expected until 1988. The complexity of the task is one factor contributing to this delay: NORPLANT<sup>R</sup> is the first example of a device releasing steroids over a protracted time period and substantial amounts of data had to be collected over the five-year lifetime of the device. In addition, the FDA has recently changed its regulations regarding NDA submissions. These changes required significant reanalysis of extensive amounts of data. A shortage of staff with regulatory experience worsened this situation and exacerbated delays. Finally, the NDA filing in the U.S. was scheduled to be on NORPLANT<sup>R</sup>-2 rods, not NORPLANT<sup>R</sup> six capsules. When a major component of the rod was discontinued by its manufacturer, however, the Population Council was left with no alternative but to reformulate the rod and modify its plans for the U.S. to register NORPLANT<sup>R</sup> capsules. This latter point has led to the most significant recent delays.

#### Recommendation

Completion of the NDA to the FDA should have high priority. More managerial control should be exercised to ensure that FDA filings are rapid and timely. The lessons learned from the NORPLANT<sup>R</sup> NDA experience should be applied to future submissions, and additional staff may be needed to carry out such activities expeditiously (see Section 3.2 for further discussion and recommendations on the introduction of NORPLANT<sup>R</sup>).

2.1.2.2 NORPLANT<sup>R</sup>-2. This method differs from NORPLANT<sup>R</sup> in that it has only two rods instead of six levonorgestrel-releasing capsules. The method appears to be as effective as NORPLANT<sup>R</sup>, but only for three years: Clinical trials that were being conducted in Chile, the Dominican Republic, Finland, and Sweden had to be terminated in the fourth year because of high pregnancy rates. Studies in the U.S. using different manufacturing lots of NORPLANT<sup>R</sup>-2 are continuing and should determine whether this problem may be related to certain lots only.

During the summer of 1987, the Population Council was informed that the manufacturer of a component of the NORPLANT<sup>R</sup>-2 rod was discontinuing its distribution. The withdrawal of this component (Medical Grade Elastomer 382) led to an interruption of the progress being made toward preparation of this method for NDA submission and has required a reformulation of the rods. It is expected that reformulation will be completed by mid-1988. Additional clinical trials will be necessary to determine pregnancy rates of the newly formulated product. It is hoped but not certain that the reformulation will enable a longer life span than three years to be achieved. Along with reformulation, mechanizing the manufacturing process of the rods will be attempted and, if successful, should significantly reduce costs of production.

#### Recommendation

Reformulation studies for NORPLANT<sup>R</sup>-2 should take a high priority, and all efforts should be devoted to this area as soon as possible.

2.1.2.3 Second-Generation Implants. Over the past two years, exploratory studies have been conducted on implant systems that will eventually have some advantages over both NORPLANT<sup>R</sup> and NORPLANT<sup>R</sup>-2 and will fill special niches in contraceptive practice. One such implant contains the steroid ST-1435. The attractiveness of this steroid lies in its lack of effect on lipoprotein patterns, its poor absorption when administered orally, and the possibility that it can be incorporated in a single implant effective for one to two years. Its poor oral absorption suggests that it may be appropriate for lactating women because little active steroid will be absorbed by nursing infants even if it is secreted in milk.

The implant with ST-1435 will be comprised of a single rod and will therefore be easier to insert and remove than either NORPLANT<sup>R</sup> capsules or rods. It is not intended to replace NORPLANT<sup>R</sup> or NORPLANT<sup>R</sup>-2, however, because it will only last 1-2 years. Dosage formulation studies are currently in progress.

To date, only a 90-day toxicity study in rats has been completed with this steroid. Therefore, before further phase II and III clinical testing can take place in the U.S., additional toxicology studies are required by the FDA.

The Council is also conducting clinical trials with the Dutch pharmaceutical firm Organon N.V. on a single implant containing 3-ketodesogestrel, which would last two to four years. To date, these trials have not been supported by A.I.D.

#### Recommendation

1) Work on ST-1435 should not be allowed to delay the key studies required for NORPLANT<sup>R</sup>-2 and the LNG IUD.

2) A first order of priority for development of ST-1435 is to start the toxicity studies required by the FDA to allow further clinical testing.

#### 2.1.3 Levonorgestrel IUD (LNG IUD)

The levonorgestrel IUD is a device that slowly releases levonorgestrel from the stem of a T-shaped IUD. The development of this device is fairly far advanced, and clinical trials have progressed over a seven-year period in several countries. Trials indicate that this is one of the most effective IUDs ever developed. In addition to its high effectiveness (less than 0.5 births per 100 women per year), this device has significant advantages over all other existing IUDs. These advantages include reduced bleeding, immediate return to fertility after removal, and reduction of dysmenorrhea.

As with NORPLANT<sup>R</sup>-2, the removal from the market of Medical Grade Elastomer 382 has delayed development, and this IUD will have to be reformulated. It is felt that the Elastomer used to reformulate NORPLANT<sup>R</sup>-2 should also be satisfactory for the LNG IUD.

The LNG IUD will probably cost more than \$5 per device, which is expensive compared to the Copper T380A. The advantages of this IUD, however, should overcome the higher cost for some women.

#### Recommendation

Because of the many advantages of this device, the development of the LNG IUD should proceed as rapidly as possible. It should, however, be done in parallel with NORPLANT<sup>R</sup>-2 rather than sequentially. A.I.D. should consider providing additional funds to enable this rapid development to occur.

#### 2.1.4 Contraceptive Vaginal Rings

The contraceptive ring is a doughnut-shaped drug-delivery system containing either a progestin or a progestin plus an estrogen that is placed in the vagina. These steroids are slowly released into the circulation by diffusion. One attractive feature of a vaginal ring is that it can be placed and removed by the woman herself. An early extensive investigation of a ring delivering levonorgestrel and estradiol showed that the ring was acceptable to women. Work on that ring, however, was discontinued in 1984 because of dosage problems. Current work on vaginal ring development has been delayed as a consequence of the removal of Medical Grade Estomer 382 from the market. Reformulated rings, using a new elastomer, are expected to be ready for clinical trials in early 1988.

Several types of rings are being developed. A ring releasing norethindrone acetate-ethinyl estradiol is probably furthest along in development. Both these steroids are widely used in oral contraceptives, are marketed in the U.S. and many other countries worldwide, and are expected to require only minimal toxicology studies to show the local effects in the vagina. Phase I and II trials are expected to take place over the next three years, with Phase III trials to begin in 1991.

Another promising ring candidate contains ST-1435, which is very effective in inhibiting ovulation and appears to have no effect on lipoprotein profiles. ST-1435 will be studied alone and in combination with an estrogen. As with ST-1435 implants, long-term animal toxicology studies will need to be under way before Phase III trials can begin with an ST-1435 ring.

A third type of ring, the progesterone-releasing ring, is being developed for breastfeeding women. Preliminary trials conducted over the past two years suggest a special role for this formulation in extending lactational amenorrhea. Progesterone is a natural product of the ovary and is poorly absorbed orally so that the amount absorbed by the nursing infant will be very small.

The possibility exists that work on too many rings may dilute efforts on other higher priority areas of development. Constraints in the area of ring development, however, are due to lack of personnel in the dosage formulation group rather than directly to lack of funds.

#### Recommendations

1) Although the best long-term hopes may be with a ring containing ST-1435, development of the norethindrone acetate-ethinyl estradiol ring should have highest priority. A ring for

lactating women would be useful per se, but does not merit high priority.

2) Work on contraceptive rings should be lower priority than work on NORPLANT<sup>R</sup>-2 and the LND IUD.

#### 2.1.5 Barrier Methods

In 1986, the ICCR decided to give top priority to developing barrier methods for women that in addition to providing protection against pregnancy, would protect against sexually transmitted diseases (STD) that cause infertility and also protect against viral agents such as herpes and HIV. Research has begun to select several agents that protect against STDs when administered vaginally and to develop new systems for the vaginal delivery of these agents.

A pharmaceutical company has provided access to an acrosin inhibitor that blocks the fertilizing activity of sperm, and another company has agreed to provide access to a series of membrane-active compounds that render sperm incapable of fertilization. Two delivery systems are also under study: a vaginal ring covered with a membrane envelope and a diaphragm that could deliver the acrosin inhibitor. A.I.D. has provided only a small amount of support to date to these initiatives.

#### Recommendation

Because this activity may dilute efforts that are already in the development process, A.I.D. should not fund this initiative at present.

#### 2.1.6 Luteinizing Hormone Releasing Hormone (LHRH) Analogues

LHRH is a hormone from the brain that controls the release of luteinizing hormone and follicle stimulating hormone from the pituitary. LHRH analogues offer several possibilities for the development of contraceptive methods for both men and women.

The Population Council has attempted to use LHRH agonists (synthetic peptides that mimic the action of LHRH) to inhibit ovulation in women. Prospects have dimmed since the last evaluation with respect to this approach. Although studies in rats, monkeys, and humans with agonists have demonstrated inhibition of ovulation, there have been some unacceptable side effects. The therapeutic range of the drug was narrow and inhibition of ovulation unreliable. Furthermore, there are serious concerns relating to long-term use of these compounds in women including intervals of chronic anovulation where normal

estrogen levels are unopposed by progesterone potentially leading to endometrial hyperplasia; intervals of hypoestrogenism leading to menopausal-like vasomotor symptoms; and the possibility of enhanced bone loss through osteoporosis.

By contrast to the poor prospect in women, LHRH analogues that cause the inhibition of testicular function in men are one of the few promising leads for the development of a reversible male contraceptive. These analogues inhibit spermatogenesis by depressing gonadotropin secretion from the pituitary and testosterone synthesis from the testis. Because LHRH agonists inhibit testosterone synthesis, in addition to inhibiting spermatogenesis, they also lead to decreased libido and the loss of the ejaculatory response. Simultaneous administration of androgen, therefore, will be necessary to eliminate these side effects. The Population Council is conducting studies on two implant systems designed to deliver, respectively, a constant amount of a highly potent agonist and a constant amount of androgen. This method is very early in the development process and a number of issues remain to be resolved, including the potential length of effectiveness, appropriate dose of androgen to avoid loss of libido or impairment of various androgen-dependent functions (e.g., protein and bone metabolism), and the reversibility of the method after use.

In addition to LHRH agonists, the Council has conducted early studies on LHRH antagonists, which competitively achieve their effects by directly blocking pituitary LHRH receptors. Work on one such compound, LHRH-22, was terminated when it was found to be associated with histamine release leading to edema. An equally potent antagonist, LHRH-34, is currently being studied which causes only minimal histamine release.

#### Recommendations

1) Acquiring convincing clinical evidence of the LHRH analog efficacy in men should be pursued with the highest priority. Collaboration of the French group (P. Bouchard) with experience in this area and the ICCR may be very expeditious and should be encouraged.

2) The new implant delivery systems for LHRH analogs and a high-potency androgen should be tested for efficacy of delivery for a minimum of one year, with a view to development of one or both implant units with longer periods of use. Longer periods would minimize intervention intervals that may be a hindrance to patient acceptability and continuation of use.

3) Monitoring for side effects of the steroid replacement regimen should give careful consideration to the degree, quality, and duration of restoring seminal vesicle and prostate functioning after withdrawal of the inducing agents.

Reassurance that the functional recovery of the testis is adequate and normal after long periods of suppression will be a necessary component of this mode of contraception.

#### 2.1.7 Inhibin

The progress made by the Population Council with inhibin over the past one to two years has been remarkable, heightening interest in this substance as an agent that may provide the first acceptable male contraceptive based on an endocrine suppression mechanism that selectively suppresses FSH secretion and does not suppress LH mediated androgen production.

Over the past decade, intense efforts have been undertaken by numerous laboratories to isolate inhibin. During 1985-86, an A.I.D.-funded Population Council project collaborating with investigators at the Florida Institute of Technology and the Salk Institute succeeded in isolating sufficient amounts of inhibin from ovine rete testis fluid to permit its characterization. This was the first reported purification and partial characterization of male inhibin. With the availability of the highly purified ovine testicular inhibin, plus other substances, it then became possible to conduct a variety of anatomic and physiologic experiments. Although it appears that the mechanism of action of inhibin is more complex than at first envisioned, the lead remains promising, justifying further study regarding the chemistry and physiology of inhibin. These, however, must await development of a means of producing large amounts of pure inhibin.

The Population Council has begun a significant effort aimed at the production of inhibin by recombinant DNA technology. When sufficient material is available, the problem of a long-term mode of administering inhibin-derived contraceptive peptide(s) must be addressed, perhaps through the implant system presently being devised for the delivery of LHRH agonists.

#### Recommendations

1) A.I.D. support should be provided to permit a significant effort aimed at the production of inhibin by recombinant DNA technology. In particular, a priority effort should be made to complete the cloning and characterization of the cDNAs for the human beta-A inhibin subunit and to develop mammalian cell expression systems.

2) Studies on the optimal conditions for the biological expression of inhibin in gonadal cells and physiological studies of inhibin-activin effects should follow as the next level of priority.

3) When sufficient material is available, the problem of a long-term mode of administering inhibin-derived contraceptive peptide(s) must be addressed.

2.1.8 Other New Leads

2.1.8.1 Gonadotropin Surge Inhibiting Factor (GnSIF).

Efforts over the past 12 months have been directed to studies to isolate GnSIF from porcine follicular fluid. This effort is based on a number of biological studies performed over the past eight years that suggest there is a peptide in porcine and human follicular fluid--designated gonadotropin surge inhibiting factor--that will inhibit the surge of LH secreted by the pituitary in response to LHRH. The Population Council is working in collaboration with Eastern Virginia Medical School in these efforts. Present evidence suggests that GnSIF is a small peptide that could be used as a nonsteroidal form of contraception inhibiting ovulation. The product isolated, however, is still insufficient in purity, character, and amount to provide a true sense of the identity to GnSIF.

Recommendation

Until a pure protein/peptide product having the desired biological activity is isolated, characterized, and produced, A.I.D. should withhold significant funding.

2.1.8.2 Anti-LHRH Vaccine. LHRH is a 10-amino-acid peptide made by the brain that regulates the secretion of LH and FSH. Neutralization of LHRH by antibodies is known to reduce the secretion of pituitary hormones and produce infertility in animals. This principle forms the basis of an LHRH vaccine. Studies by the Population Council have also shown, however, that male rats, rabbits and monkeys immunized against LHRH will experience a decrease in testosterone secretion, and therefore androgen supplementation will be required. The androgen implant being developed at the Council for use with LHRH analogues should provide an elegant mode of androgen administration for up to one year, if the vaccine is proven suitable for human use. The anti-LHRH vaccine appears to require a considerable amount of further study at the probing level before A.I.D. support would be warranted, particularly in times of limited budgets.

Recommendation

No significant investment of A.I.D. funds for an anti-LHRH vaccine is warranted at this time.

2.1.8.3 Antisperm Vaccine. The Population Council has conducted basic probing studies that are aimed at developing an antisperm vaccine. They are attempting to identify sperm antigens that when used to immunize women would elicit an immune response that would block fertilization. These studies are being done in collaboration with the National Institute of Immunology in India and to date have not been supported under the Population Council Cooperative Agreement.

On the basis of 20 years of reports on this approach, the expectation is that this may prove to be a long-term, costly, and high-risk commitment. Before a significant A.I.D. investment is warranted, therefore, this approach must document the proven identity of one or more sperm antigens directly and causally associated with a critical fertility mechanism, demonstrate that an immunological method exists for inducing effective antibody levels at the relevant reproductive tissue site, and provide reassurance that immunopathological sequelae are not a problem with the desired long-term use of this method.

#### Recommendation

Studies to develop an antisperm vaccine are at too preliminary a stage to warrant A.I.D. funding through this cooperative agreement.

#### 2.1.9 Summary of Recommendations for Contraceptive Development

1) Reformulation studies for both NORPLANT<sup>R</sup>-2 and the LNG IUD should take the highest priority. All efforts should be concentrated on these areas as soon as possible. This may involve increased funding and manpower.

2) Work on the ST-1435 implant should not be allowed to delay the key studies required for NORPLANT<sup>R</sup>-2 and the LNG IUD. A first order of priority for ST-1435 is to start the toxicity studies required by the FDA on this compound.

3) Work on contraceptive rings should have a lower priority than that on NORPLANT<sup>R</sup>-2 and LNG IUD. Among the rings, priority should be given to the norethindrone acetate-ethinyl estradiol combination. If the current version fails, effort should be focused on ST-1435. If this fails, the whole approach should probably be reevaluated.

4) A.I.D. support should be provided to assist in production of inhibin by recombinant DNA technology.

5) A.I.D. funds should probably not be provided at this time for research on barrier methods, as these might dilute other

efforts, or for GnSIF, anti-LHRH vaccines, or antisperm vaccines, which are still in too preliminary a phase.

## 2.2 Staffing and Funding

### 2.2.1 Staffing

A number of problems have arisen during the project period, many of which have been beyond the control of the Council and have hampered the progress in several areas of product development. First, the FDA decision to change the regulations for NDA filings at a point when the application for NORPLANT<sup>R</sup> was nearly complete has meant that all the studies have had to be re-analyzed according to a standard format and that more information on adverse reactions has had to be supplied. Second, the FDA has changed its regulations with regard to toxicology studies, which means a delay for development of products using ST-1435. Third, Dow Corning withdrew from distribution Medical Grade Elastomer 382, a component of the core used in NORPLANT<sup>R</sup>-2, the LNG IUD, and contraceptive vaginal rings. The withdrawal was occasioned in mid-1987 when a catalyst used in making this component was suspected to be teratogenic and carcinogenic when given in extremely high doses to laboratory rats and mice. Although further evaluation of the data from various studies have indicated that use of this elastomer posed no risk for humans, the delay has represented a major setback for these methods. These developments have meant an extra workload in several areas and raise some questions as to whether current staffing levels are adequate to move the work forward as expeditiously as desirable.

Specifically, staff seems to be short in the areas of regulatory filing, clinical trial monitoring, dosage formulation, and toxicology. With regard to preparation of FDA filings, the delay in getting FDA approval for NORPLANT<sup>R</sup> is limiting or delaying its introduction worldwide. More staff to oversee monitoring of ongoing clinical trials on NORPLANT<sup>R</sup> might also have been helpful in providing the information needed earlier by the FDA. As the programmatic emphasis continues to shift to clinical trials, additional staff will be required to ensure that they are properly monitored.

Dosage formulation has been another problem area, particularly because the withdrawal of Medical Grade Elastomer 382 has meant that three products have had to be reformulated. In the urgency to reformulate the NORPLANT<sup>R</sup>-2 system, work on the LNG IUD has temporarily been put on hold. Development of new and improved formulations/delivery systems is a continuum, and it is unlikely that this aspect of the work will be scaled down in future. With the heavy emphasis on delivery systems for delivery

of all the leads in the pipeline, this could become a critical bottleneck within the foreseeable future.

### 2.2.2 Funding

A.I.D. funding for the contraceptive development program has remained relatively constant over the last three years and has accounted for about half the Council's expenditures in this area (50 percent in 1986 and 60 percent in 1987). A.I.D. has exercised fairly tight control over the program, requiring line item approval of both major activities and individual probing studies.

The prospect of funding being provided from other sources, however, is becoming increasingly problematic. Foundation support, once an important factor, is drying up; an endowment, which now covers five percent of the budget, will probably not be increased substantially, and because the Council's goal is to provide contraceptives at the lowest price possible, licensing agreements can not be expected to provide substantial revenues.

## 2.3 Conclusions and Recommendations

### Conclusions

Staffing shortages threaten to delay the completion of products now under development. Before new staff can be hired, however, two problems must be addressed: how to enlarge the physical facilities now available to house staff and how to identify additional funding sources. The Population Council maintains a unique public sector contraceptive development effort that works in partnership with private industry as needed. With the continuing withdrawal of the pharmaceutical industry from the contraceptive R & D field, the maintenance and even expansion of this program is of high priority for population program resources. Progress under this program is hampered by inadequate financial support of the Population Council's program. Stability of funding is particularly important to the Population Council, as contraceptive development is a long-term commitment and the maintenance of a highly qualified multidisciplinary team is essential to the process.

### Recommendations:

Overall funding should be increased in stepwise fashion over the next few years: by about 50 percent over the current level of funding. Specifically,

1) A.I.D. should underwrite the costs of increased staff levels to reduce the time to market for products now in the development phase.

2) Line-by-line funding for major activities, for example, NORPLANT<sup>R</sup>, NORPLANT<sup>R</sup>-2, and LNG IUD, is appropriate.

3) A.I.D. should allocate a certain percentage (say 10 percent) of the total budget for probing studies and permit the contraceptive development program of the Population Council to decide how to allocate the funds among the new leads. This would allow flexibility to respond to changing circumstances.

4) The Population Council should develop a long-range plan specifying its view of the optimal size of the organization and optimal accommodation for such an organization (funding considerations aside). Such a plan could prove a useful management tool for solicitation of new funding.

### 3. CONTRACEPTIVE INTRODUCTION

### 3. CONTRACEPTIVE INTRODUCTION

#### 3.1 Overall

In 1983, the Population Council formally initiated a new program designed to support the carefully planned and systematic introduction of new contraceptives it was developing. This effort was to be supported in part through the Population Council cooperative agreement. To date, funds have been used for the introduction of NORPLANT<sup>R</sup> and the Copper T380A. Costs for NORPLANT<sup>R</sup> have been over \$1 million annually for the past three years, with A.I.D. providing 50, 67, and 65 percent of the total respectively. Expenditures for the Copper T380A have been considerably lower (i.e., \$217,490 for 1986 and \$169,000 for 1987), with A.I.D. funding respectively 95 and 97 percent of the effort. Overall, the high quality of the Population Council's introduction activities is impressive.

#### 3.2 NORPLANT<sup>R</sup>

##### 3.2.1 Progress to Date

In 1983 the Population Council initiated a program to introduce NORPLANT<sup>R</sup> into family planning programs around the world. The introduction of NORPLANT<sup>R</sup> has proceeded slowly and deliberately, with about 50,000 users to date in clinical field trials. There is considerable interest in the method, with pre-introduction clinical evaluations complete or ongoing in 26 developing countries, and a number of others having expressed an interest in the system.

At this point, 12 countries have approved NORPLANT<sup>R</sup> for commercial or programmatic introduction: Finland and Sweden in Europe; Chile, Colombia, Ecuador, the Dominican Republic, Peru, and Venezuela in Latin America; and China, Indonesia, Sri Lanka, and Thailand in Asia. There are over 100,000 users now in Indonesia alone in the national family planning program.

The Huhtamaki Oy/Leiras Medica pharmaceutical company, the Finnish company that has exclusive license to manufacture the implants, is responsible for all registration efforts overseas. Leiras has filed for registration in several other countries in addition to those listed above but, because it is small, often works through other organizations to achieve product registration. Consideration needs to be given on how to accelerate the registration process. To a certain extent, the pace of approval, and therefore of introduction, may have been affected by the failure to date of the FDA to approve this method for U.S. use (see Section 2.1.2.1). It is expected that an

application will be filed by June 1988 and approval may be given as early as late 1989.

Because NORPLANT<sup>R</sup> is a new method and because it has not yet been approved for use in the U.S., the Council is taking considerable care with the introductory activities, proceeding with a deliberate pace to ensure that no mistakes occur that might result in major setbacks to the program.

### 3.2.2 Introductory Activities

The introductory activities include training, development of materials, the conduct of user perspective studies, and the development of relationships with local service-providing organizations to offer the contraceptive. Progress in these areas is described below.

#### o Training

Training facilities have been established in Indonesia and Santo Domingo, and two others are expected to open soon in Egypt and Brazil. Some 700 Thai physicians have been trained, and training projects are being explored with leaders in Ecuador and Colombia.

#### o Materials

Materials are being developed for several audiences: service providers, including physicians and counselors; clinic managers; and prospective and actual users. Collaborating with the Population Council in developing these materials has been Leiras, PIACT, AVSC, and FHI.<sup>1</sup>

#### o User Perspective Studies

A unique aspect of this introductory effort has been the considerable emphasis on user perspective studies. On the basis of a model developed in Brazil, a survey was undertaken in the Dominican Republic and another is under way in Mexico. Studies are ongoing in Kenya and in Zambia, and one is planned in Indonesia. FHI is undertaking surveys in nine countries and PIACT in four. These studies focus on the introductory approaches for NORPLANT<sup>R</sup> as well as the acceptability of the method itself. Both surveys and focus group studies underline the importance of good provider support. In Brazil, the overwhelmingly positive responses of users has been helpful in

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<sup>1</sup>See glossary for the full names of these and other organizations mentioned in the text.

convincing authorities of the value of the method and the safety of the clinical trials.

o Assuring an Adequate Infrastructure

Developing the infrastructure to provide the method is expected to be a problem, particularly in Africa. The Council is exploring the possibility of incorporating NORPLANT<sup>R</sup> into services in Kenya, the first country to be involved, and lessons learned are expected to be transferable as other African countries become involved.

An important key to the success of the worldwide introduction program will be increasing the involvement of other donor agencies, many of which are already part of the inter-agency task force that has been involved in development of the training, materials, development, and user perspective studies activities described above. In particular, as the Population Council increasingly relinquishes its custodial role over NORPLANT<sup>R</sup>, it will be important for donor agencies (the World Bank and UNFPA) and service delivery organizations (IPPF, FPIA, AVSC, and The Pathfinder Fund) to take a lead role in backstopping local service delivery organizations.

3.2.3 Constraints

An important constraint has been the small size of the Population Council field staff involved in introduction activities. In contrast with private drug companies, which spend tens of millions of dollars and sometimes have staffs of hundreds, the Population Council's staffing for this introductory effort has been very modest. A small full-time staff at headquarters is complemented by two medical representatives, one in Asia and the other in Latin America. In Africa, however, where the challenge is greatest, provision of a medical representative is still only at the planning stage.

In addition, the high cost of NORPLANT<sup>R</sup> has been a deterrent to its broader introduction in some of the countries where it is approved. Its cost (public sector price at least \$15.00 and as high as \$32.00 in some countries) is caused by the necessity for hand manufacture. Because of the high initial cost of the implants, A.I.D. support for purchase of supplies is critical. A.I.D. policy, however, is not to purchase for widespread distribution non-FDA approved drugs or devices and therefore, unless alternate donor agencies can be identified that will be willing to bridge the minimal two-year gap before anticipated FDA approval, widespread introduction will continue to be delayed.

#### 4. FAMILY PLANNING PROGRAM COMPONENT

### 3.3 Copper T380A IUD

In contrast to NORPLANT<sup>R</sup>, the Copper T380A has enjoyed rapid introduction, in considerable part because it has FDA approval and can therefore be purchased by A.I.D.

In 1983 the Council and PIACT began development of a package of prototype training and informational materials, designed to support the introduction of this method. These packages were distributed to family planning leaders around the world and played a significant role in the incorporation of this advanced device into ongoing programs. Approximately 5 million Copper T380A IUDs have now been distributed in 30 countries. Building on these materials and the insight gained in the introduction of NORPLANT<sup>R</sup>, the Council, PIACT, and other agencies have begun model country-specific needs assessment and training projects. The imminent reintroduction of the IUD on the U.S. market should be very important in stimulating the use of these devices in developing countries.

#### Recommendations

1) The Population Council should work closely with Leiras to ensure that each country's product registration activities go forward with as little delay as possible.

2) A.I.D. should consider waiving the current policy relating to distribution of non-FDA approved drugs and devices. If this cannot be done, A.I.D. should consider increasing distribution of NORPLANT<sup>R</sup> on a research basis.

3) The Population Council should seek non-A.I.D. funding to purchase large numbers of NORPLANT<sup>R</sup> sets for the Contraceptive Introduction program. In particular, support should be sought from donors that do not require FDA approval prior to purchase and distribution of contraceptives, that is, the UNFPA, the World Bank, and foundations.

4) The Population Council should ensure that in-depth documentation of contraceptive introduction activities, including user perspective studies, is undertaken and that such information is broadly disseminated to workers in the population and family planning field.

5) Increased funding should be considered to accommodate a larger field staff, particularly for one or two persons in Africa.

6) The Population Council should seek to increase involvement of major service delivery programs, donors that support such programs, and technical assistance agencies in their contraceptive introduction activities. Principal agencies with which greater involvement should be sought include the World Bank, UNFPA, IPPF/WHIR, JHPIEGO, Pathfinder, FPIA, and AVSC.

#### 4. FAMILY PLANNING PROGRAM COMPONENT

##### 4.1 Overview

The purpose of this component of the cooperative agreement is to allow the Council to provide assistance to family planning service delivery efforts through the conduct of field-based projects, technical assistance and other activities that build on the Council's prior family planning research, evaluation, and policy development activities worldwide.

Activities under this component include operations research, technical assistance, exploration of new programs, and production of information and educational materials. Overall, the Council's selection of projects under this component has been appropriate and in accord with the Council's own goals. The goals met through this activity have included 1) expansion of low-cost contraceptive availability through conducting operations research and research evaluations; 2) developing local capacities and infrastructures; and 3) discovering more about the relationship between family planning and HIV information and prevention activities.

##### 4.2 Programs by Region

The Council has long been active in Latin America and Asia, and more recently in Africa. Overall, it has done an impressive job in carving out an apparently unique role in establishing long-term technical assistance and institution-building relationships with numerous national family planning programs in these areas. Particularly notable has been its performance developing service statistics, management information systems, and program research and social science investigatory capacities.

##### 4.2.1 Latin America

The lowest emphasis in the family planning program component of this cooperative agreement has been in Latin America, where most of the Council's extensive operations research activities are carried out through a separate A.I.D. contract (INOPAL). Activities have included a natural family planning operations research project in Colombia; a cost-benefit study of family planning programs in Mexico; the videotaped documentation of a community-based distribution operations research program in Colombia; two HIV and family planning operations research projects in Peru; and partial support for the operational costs of the Council's country office in Bogota.

In terms of the Council's own priorities, the two HIV operations research projects in Peru are particularly notable, as they are at the cutting edge of field research on whether and how family planning services can be successfully linked with HIV information and prevention activities. By contrast, the support for the Bogota office, which has been carrying out operations research since 1972, seems somewhat anomalous because after June 1988 all of the office's work will relate to the INOPAL project.

The Council's long-standing presence in Latin America, its operations research experience and track record, and the presence of a field structure to manage its regional programs, however, all represent a considerable resource for A.I.D. and the international family planning community.

#### 4.2.2 Asia

In Asia, mission buy-ins have been the principal funding source for the family planning program component, having financed major research studies in India and in Bangladesh. Of special importance has been the research decision-making model developed in Bangladesh, which has directly influenced national family planning program policy structure and management in that country's particular bureaucratic setting. Council staff are now engaged in documenting the model that has evolved there and exploring potential applications in other countries with similarly weak infrastructures and rigid bureaucracies, particularly in Africa.

#### 4.2.3 Africa

Most of the central funds under the family planning program component have been devoted to work in Africa, and this support has been crucial to the development, expansion, and maturation of the Council's overall sub-Saharan Africa program. Although the Council relies on several funding sources for sub-Saharan Africa activities, A.I.D. cooperative agreement funding for headquarters staff time, travel, in-house projects, and selected subawards to local African institutions has provided the wherewithal and flexibility needed to forge a comprehensive strategy in this region. The initiatives in Africa have been of three types.

##### o Exploratory Program Development

This has involved exploratory trips to Nigeria, Kenya, Zaire, Zimbabwe, Rwanda, Zambia, and Mali, during which needs have been assessed, priorities identified, and a strategy developed. At this point, field staffing and management structures, while still being evolved, are well positioned to

develop and support programs in Africa. An extensive network of institutional and professional relationships has been cultivated and is ready to be tapped. These are major accomplishments for a difficult region and the momentum of this effort should be sustained.

o Operations Research

The Council has demonstrated, with projects in Zimbabwe and Zaire, its ability to develop and undertake operations research in sub-Saharan Africa. In Zimbabwe, as the Zimbabwe national family planning program looks to future sustainability, the Kubatsirana project is testing potentially lower cost alternatives to the national community-based contraceptive distribution program. The Kananga project in Zaire will be critical in measuring demand for contraception in rural areas and testing pilot approaches in meeting and increasing demand.

o Technical Assistance

The Council has carved out an apparently unique role in establishing long-term technical assistance and institution-building relationships with numerous fledgling family planning programs to assist them in institution building and development of service statistics and management information systems. For example, assistance has been provided to Rwanda and Mali to develop family planning service statistics systems and a resident advisor has been provided in Zambia to develop a broad range of family planning programs. A major new project has been initiated in the Sahel region in conjunction with the Sahel Institute to provide evaluation and research technical assistance to its nine member countries. The Council has also worked with institutions in a number of African countries to build their capacity to undertake training and perform research, most recently with universities of Zimbabwe and Kenya.

The Council has also provided a substantial amount of short-term assistance in sub-Saharan Africa. For example, in 1986, assistance was given to two Nigerian states to develop their statewide five-year plans for expanding family planning services. These plans will serve as prototypes for the development of plans in other Nigerian states.

From the Council's perspective, emphasis will continue on sub-Saharan Africa, on the relationship between STDs and family planning programs, and on transferring lessons learned in Bangladesh to Africa. In addition, the Council plans to investigate the relationship of the quality of family planning care with increased contraceptive usage and to seek new ways of delivering and expanding use of family planning and health services during the postpartum period.

#### 4.3 Management

The Council's professional staff in New York and the field have a well-deserved reputation for high-quality commitment and productivity. The Council has an extensively developed field network to which substantial authority has been delegated. Although only a small portion is supported under the cooperative agreement, the project has benefited greatly from its expertise.

In recent years the Council has devoted considerable attention to developing its management resources for sub-Saharan Africa. The Africa program is currently staffed by four New York-based professionals. The Council's largely successful effort to develop an effective management structure for sub-Saharan Africa, primarily with non-A.I.D. funds, is in alignment with A.I.D.'s own priority on Africa.

The Council's intention, however, is to delegate management responsibility for the sub-Saharan program to the field. Two resident advisors have been selected in Zambia and in Mali, and the Council is presently negotiating with the governments of Kenya and Senegal to establish a presence in those countries. It expects to place a senior representative in Nairobi by the end of 1988, with a subregional office to be opened in Senegal in April 1988.

Overall, the Council is doing a good job in managing the workload of the cooperative agreement and completing projects in a timely manner. The only area where there appeared to be some minor problems was with regard to reporting format and liaison with A.I.D. The Council and A.I.D. should work together to develop an annual reporting format that is responsive to the needs of both agencies and to develop trip reporting guidelines that can be incorporated into the next cooperative agreement.

#### 4.4 Assessment of Value of Family Planning Component to A.I.D.

The overall conclusion is that A.I.D.'s support to the Council for the family planning programs component of the cooperative agreement has been extremely productive and worthwhile.

Several interrelated factors justify this broad endorsement of the Council's family planning programs work. First is its track record. The Council's approach produces results that have made a difference to field programs. Second, the Council is a unique resource in the world with its extensive field structure, its multidisciplinary approach to program development and research, and its highly professional and qualified staff. This component of the cooperative agreement

gives both A.I.D./Washington and USAID missions the ability to tap into a formidable and unparalleled resource. Third, insofar as the family planning programs component is essentially a field-based operation, it helps to keep the Council's work in the other vital areas of contraceptive development and introduction well informed and directed by programmatic needs, constraints, and imperatives. Fourth, the Council's family planning programs' work has been responsive to A.I.D.'s own changing priorities over the years (e.g., sub-Saharan Africa, natural family planning, HIV). Finally, the Population Council is one of the very few international population agencies that has the capacity with its field structure and multidisciplinary focus to provide long-term technical assistance to national family planning programs in the areas of institution building, research, service statistics, and management information systems. It did this successfully in the past in Asia and Latin America, and it has laid solid groundwork for doing the same in several sub-Saharan African countries where national family planning programs are in their earliest stages of development and in need of careful, professional nurturing.

Recommendations:

o General

1) The next cooperative agreement between A.I.D. and the Population Council should continue explicitly to include and fund the Council's important work in the family planning program area.

o Latin America

2) A.I.D. should consider providing short-term support for the Council's Bogota office until a decision on the Latin America operations research contract is reached. The Council should consider including support for that office in its next proposal for the operations research contract.

3) Under the next cooperative agreement, the Council should continue to be allowed to respond to worthy targets of opportunity in Latin America that cannot be supported by A.I.D. through other mechanisms, or where the Council clearly has the expertise and capacity to delivery quality results in timely and cost-effective ways.

o Asia

4) Although it seems unlikely that scarcer central A.I.D. funds will be allocated for the Council's family planning program activities in Asia, it is recommended that the Council retain the capacity to use central A.I.D. funding in Asia for mutually agreed-on, highly important leverage projects and activities.

5) The Council should pursue its plan to adapt the Bangladesh model to other settings and to document the system and publish results so others can also benefit from the experience.

o Africa

6) Under a new cooperative agreement, A.I.D. should continue to provide flexible funding to the Population Council for its sub-Saharan Africa family planning program activities so that the Council can maintain and accelerate its forward momentum in the region.

7) A.I.D. should continue to fund and utilize the Council's extensive capacity to undertake in sub-Saharan Africa family planning program evaluation and operations research.

8) In the next cooperative agreement, the Population Council's long-term technical assistance and institution-building role in sub-Saharan Africa should be explicitly recognized and supported through the allocation of funds for these activities.

## 5. PRINCIPAL CONCLUSIONS AND RECOMMENDATIONS

## 5. PRINCIPAL CONCLUSIONS AND RECOMMENDATIONS

### 5.1 Conclusions

A.I.D.'s support to the Population Council for contraceptive development, contraceptive introduction, and family planning program development has been extremely productive and worthwhile. The Council has been one of the most successful public sector programs in the contraceptive development field and has indeed gotten more new methods to the marketplace than any other program. A.I.D. support has been critical in ensuring continued progress by the program and has been a most successful investment as judged by both actual and potential returns. The quality of the research performed, both basic and applied, has been exceptional.

The development and introduction of contraceptives is a very expensive and long-term endeavor. Over the recent years, A.I.D. has contributed approximately 50 percent of the total support to the Population Council's contraceptive development program, which indicates the large extent to which this program is dependent on A.I.D. support. In the past, support was provided also by the Rockefeller, Ford, and other foundations. These sources are now providing funding on only a minimal level, and therefore A.I.D. support will become even more important if many of the leads in the pipeline are to become a reality.

The Population Council maintains a unique public sector contraceptive development effort. With the continuing withdrawal of the pharmaceutical industry from the contraceptive R & D field, the maintenance and even expansion of this program is of high priority for population program resources. At present, not all new leads can be pursued because of both funding and staffing constraints. These constraints are particularly apparent in certain key areas of the development process such as dosage formulation, toxicology, regulatory affairs, clinical affairs, clinical trial coordination and monitoring, and field staff for introduction activities. If a number of contraceptive development tasks had to be carried out simultaneously, such as writing and compiling two or three NDAs, funds and staff would be a serious constraint and cause delays.

### 5.2 Recommendations

Three principal recommendations arise from the conclusion that the work of the Council deserves continued and expanded support:

- 1) A.I.D. funding should be increased in a stepwise

fashion over the next few years by about 50 percent over the current level of funding.

2) Additional staff should be recruited in several key areas related to product development, registration, and clinical trials to reduce the time to market for products now in the development pipeline.

3) The Population Council should develop a long-range plan specifying its view of the optimal size of the organization and optimal accommodation for such an organization (funding considerations aside). Such a plan could prove a useful management tool for solicitation of new funding.

Other principal recommendations include the following:

4) A.I.D. should continue its policy of line-item funding for the key major activities being supported such as NORPLANT<sup>R</sup>, NORPLANT<sup>R</sup>-2, levonorgestrel IUD, and vaginal ring studies. For flexibility and easier administration, however, a certain percentage (about 10 percent) of the total contraceptive development budget should be allocated for probing studies, and the Population Council should be allowed to decide how to allocate funds among them.

5) A.I.D. should increase funding for the contraceptive introduction program to permit recruitment of additional field staff, particularly one or two persons for Africa.

6) The Council should work closely with Ieiras to ensure that each country's product registration activities for NORPLANT<sup>R</sup> go forward expeditiously.

7) The Council should seek greater involvement in their contraceptive introduction activities of major service delivery programs, donors that support such programs, and technical assistance agencies.

8) A.I.D. should maintain the capability to take advantage of the Population Council's field experience and expertise by continuing to support the family planning program component of the cooperative agreement.