International Cooperative Biodiversity Groups

Program Review Report

14-16 January 2002

Executive Summary

The Fogarty International Center (FIC) commissioned this review of the International Cooperative Biodiversity Groups (ICBG) program as it nears the completion of its second award cycle. The objective of the review was to advise FIC and its interagency partners as to whether the ICBG program continues to meet its sponsor's several, interrelated goals and objectives. Initiated in 1993, the ICBG Program is a unique effort that addresses the interdependent issues of drug discovery from natural products, biodiversity conservation, and sustainable economic growth.

The ICBGs are public-private, multi-national consortia funded by cooperative agreement awards from FIC, other components of the National Institutes of Health (NIH,) the US Department of Agriculture, and the National Science Foundation. The NIH institutes participating are the National Cancer Institute, the National Institute of Allergy and Infectious Diseases, the National Institute of Mental Health, the National Institute on Drug Abuse and the the National Heart, Lung, and Blood Institute.

The reviewers are convinced that the ICBG program should continue and be expanded. The ICBG program concept of combining drug discovery with conservation and economic development represents a critically important approach both for identifying new drugs and other products from natural sources and for assuring fair and equitable distribution of benefits from bioprospecting. The next round of grants must build on the 9 years of experience in the program. Given the information and time available for the review, the reviewers felt that they could not with complete confidence answer the question, 'Does linking conservation, economic development, or drug discovery in the ICBG program or in a given grant improve the probability of success across the spectrum of goals?'. Nonetheless, the reviewers are convinced that the ICBG program shows every indication that it is a successful experiment. There are many examples of achievements including and arising from the processes used to implement the conceptual basis of the ICBGs. For example, the number of species collected and screened in drug discovery efforts since the onset of the program is impressive. Moreover, the ICBGs have done an outstanding job in establishing agreements that define potential benefits and how the benefits from drug discovery will be allocated. Indeed, the ICBG program is leading the effort worldwide to implement the principles of the Convention on Biological Diversity. The ultimate goal of the ICBG program is to assure that when an ICBG grant ends, the scientific, technical, operational, and infrastructure capacities for sustaining drug discovery, related conservation and economic incentives are established in the host countries and remain conceptually linked. If this objective is met it would be, in itself, sufficient justification for the investment of resources by FIC and its partner agencies.

Recommendations for shaping and maturing the ICBG program over the next five to ten years emerged from the review. The reviewers made the following recommendations:

- ✓ Drug discovery, conservation and economic development should continue as the core elements of the ICBGs.
- ✓ Drug discovery should continue to be the first among three equal goals of the ICBG program, with conservation and creating economic incentives for drug discovery given the emphasis required so that they too will be legacies of the ICBG program.
- ✓ ICBG policy should be to fund new grants in two phases: First a planning phase in which grantees establish the fundamental structure and substantive national and local contributions in planning for the ICBG in the host country. Second, an implementation phase to carry out the plans developed in the first phase.
- ✓ ICBG grants should include a ”business plan” that defines the economic incentives for benefits sharing; agreements, procedures and policies for equitable sharing; and a process whereby the local program will become self-sustaining.
- ✓ Given the importance of the ICBG experiment FIC should commission a comprehensive analysis of the 1993-2002 ICBG program to determine what has worked and how, and what has not worked and why.

The reviewers also provided some answers to focus questions posed by the program officials regarding specific decisions for management of the program.

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Panel of Experts

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National Institutes of Health

Fogarty International Center

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I. Introduction and Context of the ICBG Program Review

The Fogarty International Center (FIC) initiated the International Cooperative Biodiversity Groups (ICBG) grant program in 1991. The ICBGs seek new drugs and other uses from natural products. The ICBGs are unique in that they also work to integrate conservation and economic growth into their drug discovery efforts. The ICBGs are funded by grants from FIC, other components of the National Institutes of Health (NIH,) the US Department of Agriculture, and the National Science Foundation. The grants are awarded for five years and the second round of grants is expiring. FIC managers are considering whether to continue the ICBG program and assessing the goals and scope of the program should it be continued. The other federal institutes and agencies are also evaluating the ICBG program to assure that it is meeting their missions and priorities in drug discovery, promotion of agriculture, biodiversity conservation, and the advancement of science.

The FIC organized a review of the ICBGs to provide an independent set of observations and recommendations. The primary purpose of the review was to advise as to whether the ICBG program continues to meet its sponsors' several, interrelated goals and objectives.

Drugs derived from plants and other natural products continue to make up a major part of the pharmacopoeia of allopathic medicine. Traditional medicine practiced by indigenous peoples in undeveloped areas relies almost exclusively on locally available natural products for use in treating disease and other health conditions. Herbal medicines have an important role across the range of medical practices worldwide and the use of herbal products is growing in the west. Natural products still have a vast potential as a source of medicines. Neither have they been fully explored for broader application in animal health, nutrition, agriculture or other beneficial uses. Thus it would seem that biomedical researchers from academia, pharmaceutical companies, and research entrepreneurs would be rushing to find new drugs in natural products. At the same time their counterparts from veterinary medicine, agriculture sciences, and elsewhere would be evaluating the same resources for their own purposes. In fact this research is progressing at a slower pace than might be expected. There are several intersecting, complicating factors that impede drug discovery and other uses of natural products. Among these are difficult scientific, logistical, economic, social and cultural, and political problems.

There are millions, if not tens of millions, of species among the plants, insects, animals, and microbes on Earth that make up the biological diversity of nature that may yield drug and other beneficial uses. Only a fraction of these have been identified and classified. Very few of the known species have been completely evaluated for beneficial uses. This diverse panorama provides a huge resource base that scientists must select from to screen for potential new drugs. Attractive leads from screening must then be proven to be a practical source of a safe and effective compound for treatment or prevention of disease, an expensive and lengthy process.

The majority of species are found in underdeveloped or undeveloped areas. The application of cutting edge scientific methods and technologies in these remote regions is logistically demanding. Drug discovery requires the application of many specialized scientific disciplines, including medicine and public health, chemistry, several biological sciences, sociology, anthropology, ecology, toxicology and pharmacology, statistics, and informatics. Convening multidisciplinary groups is not

easy in modern research institutions and is much more difficult in remote areas where the expertise must be drawn from both local and foreign sources. Maintaining the cutting edge of science in drug discovery from natural products also demands remaining abreast of rapid progress in biomedical research in genetics, genomics and proteomics, combinatorial chemistry, and advances in development of synthetic drugs.

Species, habitats, and genetic biodiversity are being lost at a rapid rate across the globe. The loss is due to resource development, climate change, agricultural and industrial practice, and other stresses. At the same time that diversity is being lost, social change and disruption among indigenous people leads to loss of traditional knowledge of the properties and uses of local natural products for medicinal and other purposes. The result is an irrevocable disappearance of species, habitats, and genetic resources that are invaluable in their own right and should be conserved, and the concomitant loss of their potential for improving human health and well being.

Conflict between the desire to conserve habitats rich in biodiversity and development of these areas for commercial, industrial, agricultural, mining, or similar uses creates difficult economic and social equity questions. Drug discovery from natural products is affected by the outcome of the debate addressing these questions and to a limited extent helps frame the questions. Drug discovery is clearly less probable if species are lost to development. But it is not possible to assure that conservation of species to permit drug discovery will bring the level of benefit realized by other developmental uses of the habitat areas. Typically, from the developing country perspective, the economic benefits from commercial or agricultural development of unique habitats would be viewed as a significant benefit to the national economy and perhaps to the local community. Drug discovery and conservation do not compete well by comparison.

There are tensions between who benefits from and who pays for conservation and drug discovery. For example, if the search for a drug used to promote the health of people in the area where the natural product exists is successful, then the local benefit is greater. However, because the diseases that affect indigenous people in remote areas and the populations of developing countries are not the same as those

causing greatest morbidity and mortality in the developed world, there are powerful economic incentives to seek drugs for the latter purpose rather than the former. The organization that manages and pays for natural product research expects to benefit both from professional recognition for an important discovery and economically from its sales.

Few developing countries have established a system of rules to govern access to and benefits sharing from development of their biodiversity. Who may enter to collect, and when, and what and how much may be removed on what terms may not be clear. Such practical matters must be resolved to avoid possible misunderstanding and conflict. Equity questions cannot be avoided and are particularly difficult when drug discovery efforts are launched in a developing country by an organization from a country with an advanced economy. While the external group may have modern technical expertise and fiscal resources needed for drug discovery, the natural products are found within the host country. Thus the host country and local population have legitimate arguments for ownership of the species and access to it. In addition, they have a legitimate claim on benefits gained from the products from the species. Benefits claimed are not limited to a portion of the profit from a drug that may be developed and marketed. They may include intellectual property rights to the genome or tangible benefits from some other product unrelated to the medicine or other beneficial use resulting from bioengineering. If local lore or knowledge is used to direct the search for a new drug, the indigenous people have intellectual property claims as their knowledge is shared. Equitable agreements on ownership, access, benefits sharing, etc. can only be established if all of the participants have a full and equal understanding of the issues. These are complex and baffling matters that have not been fully resolved in societies with long histories of scientific inquiry, advanced economies, and a large body of law. Fair agreements based on full knowledge in remote indigenous communities present another, daunting challenge to drug development and conservation.

Access, fairness and equity issues cannot be resolved effectively on an *ad hoc* basis by scientists with good intentions but limited knowledge of law and policy as they implement a project of drug discovery and conservation. Experts in

international commercial and intellectual property law and economics with experience in developing countries must be involved from the outset. This expertise is expensive and not widely available. Thus its application adds significant costs to bioprospecting and conservation projects.

The architects of the ICBG program had a good grasp of the scientific, environmental and conservation, economic, social and procedural issues that impact on and detract from successful drug discovery from natural products. They recognized these factors when the program was conceived over a decade ago. Indeed, the ICBG program was originally modeled on a concept that emerged from a conference sponsored by FIC in 1991. The concept proposed combining drug discovery, conservation of biological diversity and economic growth into a unified effort. The ICBG program is intended to test the hypothesis that including conservation and economic development in drug discovery projects will help these programs gain acceptance and be successful in developing countries. The FIC program manager and the grantees continue to stress that the ICBG program is an experiment that tests the hypothesis that a multi-dimensional project that gives balanced emphasis to conservation, economic development and drug discovery will assure that progress made toward any one of these goals will support the progress toward the other two. This conceptual approach contrasts with the popular notion that conservation and economic gain are driven by major commercial success in drug discovery.

The ICBG program is at a critical point as the second consecutive five year grant cycle comes to an end. Substantial commitments of intellectual capital, fiscal resources, and innovation have been focused by the grantees to implement the conceptual basis for the ICBG program. As these grants were implemented and work progressed, they were expected to both test the conceptual basis of the ICBG program and to produce advancements in drug discovery, conservation, and economic development in the regions where they worked.

The reviewers were not specifically asked to discuss whether the fundamental conceptual basis for the ICBG program has been validated. But this concept of linking conservation and economic development to drug discovery and whether this

linkage improves the probability of success in the individual grants or the entire program was central to the reviewer's deliberations. Given the information provided in the briefings at the review meeting, the format of the written materials distributed, and the time available for the review, the question could not be answered with complete confidence. Recommendations for shaping and maturing the ICBG program over the next five to ten years emerged from the information provided and discussions among the reviewers and the participants. Nonetheless, the reviewers are convinced that the ICBG program shows every indication that it is a successful experiment. There are many examples of achievements including and arising from the processes used to implement the conceptual basis of the ICBGs. The reviewers earnestly hope that the ICBG program will be continued and expanded. The next round of grants must build on the 10 years of experience in the program to advance and sustain drug discovery, biodiversity conservation, and incentives for economic development. And the FIC should find the resources to commission a thorough, independent analysis aimed at determining whether the conceptual basis of the ICBG program is valid and, as importantly, to collect systematically from the grantee's efforts those achievements and tools that were created from their hard work on and innovative approach to an exceedingly difficult challenge.

This report is based on materials provided by the FIC staff describing program progress to date and presentations by current ICBG grantees and FIC and other federal agency staff at the review meeting. In addition, the reviewers met in closed session following the open meeting.

II. Consensus Observations and Recommendations Regarding the Core Conceptual Basis of the ICBGs

The reviewers believe that a programmatic focus on the search for new drugs and other beneficial uses derived from natural products is entirely appropriate and has great potential for improving human health and welfare. The effort is particularly important in areas rich with diverse biota that are threatened. The ICBG program concept combining drug discovery with conservation and economic development represents the best conceptual approach both for identifying new drugs and other

products and for assuring fair and equitable distribution of benefits from bioprospecting.

The ICBGs funded over the past decade have accepted the new conceptual approach to drug discovery and transformed it into practical, functional, productive projects that embraced and tested the concept. The next group of ICBGs should move from a set of independent projects testing approaches to implementing the concept of integrating conservation and economic development into drug discovery to a comprehensive program that advances the proven elements of the concept. This transition must be managed by FIC and its federal funding partners such that innovation and experimental approaches to the science of drug discovery and conservation by individual ICBGs are not threatened.

The reviewers suggest that the ultimate goal of the ICBG program is to assure that when an ICBG grant ends, the scientific, technical, operational, and infrastructure capacity for sustaining drug discovery, related conservation, and economic incentives have been established in the host countries. Meeting this goal will help ensure that bioprospecting and conservation will be sustained and that follow up on the drug development in the pipeline will continue. It will foster and preserve the conceptual approach linking drug development, conservation, and incentives for economic development. And it will create, test and implement mechanisms for equitable sharing of benefits with indigenous peoples and host countries that protect local knowledge and biological resources and offer tangible benefits to all participants. These objectives are in themselves sufficient justification for the investment of resources by FIC and its partner agencies.

The following recommendations and observations are intended by the reviewers to advance the ICBG program and help assure that the ICBGs establish lasting programs of scientific rigor and fundamental fairness in the host countries that offer a paradigm for other, similar efforts.

Drug discovery, conservation, and economic development should continue as the

core elements of the ICBGs.

These three goals need to be clarified, tightened and more carefully tied together. To the extent practical, conservation activities supported by the ICGB grants should relate directly to drug discovery activities. Preferably they will be driven by drug discovery needs and protection of traditional medicine practices in the host country site(s).

The term "economic incentives for drug development and for conservation" should be adopted as an alternative to "economic development." Economic incentives should recognize both the short term and long term costs and benefits of drug discovery and conservation and the distinction between who benefits and who pays. Since the goal of the ICBG program is to establish an infrastructure for drug discovery in a developing country, it is the academic institutions and scientists who are most likely to reap immediate benefits. Yet it is local communities with other, competing, and perhaps more immediate goals and incentives for use of biodiversity that make the immediate sacrifice. These communities must forego other short-term economic benefits that could come from uses or exploitation that permanently damages or destroys biodiversity and habitats. This disconnect must be addressed as the ICBG project is planned and implemented. Local governments share a critical role as participants in the planning so that the trade-offs are evaluated and managed equitably as the projects go forward. Achieving balance among the goals will require a broader range of expertise than is likely to exist in the US-based institutions participating as ICBG grantees. Grantees should first attempt to fill such gaps with experts from the host country. If this expertise is not available in the host country, the ICBGs should give priority to developing the expertise locally through training and education. The FIC proposal to support an NIH fellowship program in technology transfer is an example of an opportunity to expand local expertise necessary to the ICBG program.

Drug discovery should continue to be the "first among three equal" goals of the ICBG program with conservation and creating economic incentives for drug

discovery given the emphasis required so that they too will be legacies of the ICBG program.

The number of species collected and screened in drug discovery efforts since the onset of the ICBG program is impressive. The quality and output from the species collected and screened by the ICBGs should continue to be used as one marker of productivity in the drug discovery effort.

Although it is appropriate that drug discovery drive the ICBG program, the ICBGs should not be expected to produce a major new drug or be evaluated on this basis. The process of screening natural products for candidates for drug discovery through the many complex steps necessary to bring a major new drug to market takes at least 10 to 15 years. Thus it becomes critical that each ICBG prepare local experts to take responsibility for continuing the project. Local personnel who participate in the ICBG should be able to conduct collaborative research and to attract alternative funding sources. They must be able to manage benefits sharing schemes, write competitive grants, prepare partnership agreements with private industry, and do outreach and education. Each ICBG would leave behind, after 10 years of work, an organization that is fully prepared for finding a breakthrough drug. The local participants should be trained and equipped to assume the role as the source of national expertise and leadership in the science and policy for biodiversity protection and conservation, bioprospecting, drug discovery, and associated matters such as economic incentives and intellectual property rights.

Adopting a stronger program focus on capacity building should not be viewed as limiting the potential benefits from drug discovery. Instead, it should improve the odds for identifying medicines from natural products.

Placing an initial focus on phytomedicines in drug discovery would also help document, evaluate, and preserve local medical practices, particularly if a social sciences perspective were added to these projects. Many indigenous peoples are going to remain where the ICBG work is conducted and their local medical practices will continue to be important to their health status. Employing additional, specialized

social sciences expertise in the ICBG drug discovery effort would help preserve traditional medical practices and assist in gaining local acceptance for western medicine as an adjunct to indigenous practice. An approach that recognizes the importance of local diseases and local practices will highlight the importance of conservation and incentives for economic development at the local level. Another advantage of this approach is that it provides a role for smaller pharmaceutical firms in the host country in developing and marketing phytomedicines.

The ICBG program has demonstrated the technical difficulty involved in elucidating the chemical structures of novel bioactive compounds in natural products. Intense collaboration between US-based institutions and local scientists is necessary to establish core chemistry activities. New ICBG grant applicants (including those competing for renewal of existing grants) must demonstrate a thorough understanding of the complexities of the drug discovery process and must describe resource conservation goals that are directly linked to drug discovery. The best evidence of such understanding is a plan for drug discovery and related conservation activities that describes the processes to be followed in the proposed ICBG grant. The application should describe drug discovery from bioprospecting through *in-vivo* testing and how collaborations will be established in the host country site. Local expertise and institutions should be used where these exist in the host country and roles and responsibilities must be spelled out.

Technical and scientific methods for screening, chemistry, and testing must be standardized, state-of-the-art, and reproducible. Where capacity for screening does not exist, it should be sought from outside either from private industry or from government agencies. The plan must recognize and be consistent with host country legal, social, and political practices.

FIC policy should be to fund new ICBG grants in two phases: First, a planning phase in which grantees establish the fundamental structure and substantive national and substantive local contributions in planning for the ICBG in the host country. Second, an implementation phase to carry out the plans developed in the first phase.

As the ICBG program enters its second decade, it should reach its potential to set or model the paradigm for similar efforts to promote partnerships for public health, natural resource conservation, and incentives for economic development between developing and developed nations. Grant applicants should submit proposals that describe the entire ICBG from its onset to completion. These grants should then be funded in two phases. The first phase, proposed to last two years, would establish the basis for the full ICBG. The second phase would fund the full operation of the ICBG only if the start-up planning yields good evidence that the ICBG will succeed.

The ICBG should include host country participants as active colleagues in the planning effort wherever possible. The ICBG grantee should propose broad goals, objectives and guidelines for the project. The specific program should be designed in partnership with the host country at both the national and local levels.

In addition to activities supported in the current ICBG grants the planning phase would include:

- Identifying key individuals and local practices in the ICBG program site.
- Identifying policy makers, policies and regulations at the national level.
- Identifying the media and other institutions that are targets for outreach and education.
- Developing culturally appropriate prior informed consent agreements.
- Completing agreements for access, export, and intellectual property and benefits sharing.
- Identifying applicable expertise needed to fill gaps missing in the host country.
- Creating data management systems that are integrated with other grants and centrally with FIC.
- Establishing stronger partnerships for drug development in the grantee institution, in federal health laboratories at NIH and elsewhere to increase drug discovery opportunities.
- Establishing collaborative scientific research relationships and communications

links with other ICBGs and the FIC and its funding partners.

The second phase of an ICBG grant should be awarded when FIC staff determines that the foundation for a full program is in place and there is good probability that the full program will produce the intended purpose. It is anticipated that second phase work can begin in the third year and continue through the five-year term of the grant.

New ICBGs should plan to be renewed for a second five-year term. After ten years, the ICBG should have attained its goals. Some current grantees have participated in the program since its inception ten years ago. These grantees should not be prohibited from reapplying nor should they necessarily abandon established partnerships in the US or in host countries. However all grant applications should compete equally and adhere to any new, applicable guidelines set by FIC and its funding partners for the third round of competition.

ICBG grants should include a "business plan" that defines the economic incentives for benefits sharing; agreements, procedures and policies for equitable sharing; and a process whereby the local program will become self-sustaining.

The ICBGs have done an outstanding job in establishing agreements that define potential benefits and how the benefits from drug discovery will be allocated. However, financial rewards from drug discovery are possible but they are not assured. Moreover, any profits will accrue late in the tenure of the ICBG. Thus, the ICBGs have provided education, training, equipment, infrastructure, and technical advice and consultation as compensation benefits to host countries as an immediate benefit. In addition, some ICBGs have supported eco-tourism and other similar activities to generate financial benefits from conservation. This approach is admirable and should continue to be supported by FIC. It should, however, be supplemented by a business plan for sustaining the local program beyond the term of the ICBG project.

A business plan should emphasize the roles of the various host country participants at the local level and the activities that will create a local and national

infrastructure for drug discovery and development. Elements of the business plan should contain country-specific activities in negotiating, grant-writing, acquisition of private capital, and business development.

The business plan must define how new drug leads will be pursued and researched and then developed. This element should describe both the specific roles in science-and-technology and benefits sharing. Collaborative arrangements for following attractive drug leads involving large and small pharmaceutical firms, government, and academic laboratories should improve prospects for discovery. However such arrangements pose difficult administrative, confidentiality, and benefits sharing issues that should be addressed in the business plan.

FIC should commission an analysis of the 1992-2001 ICBG Program to determine what has worked and how- and what has not worked and why.

FIC staff and ICBG project investigators describe the ICBG program as an experiment designed to test the conceptual approach that links drug discovery with conservation and economic development. The ICBG grantees took the concept to the field. With innovation, flexibility, and determination, they tested the concept. The reviewers believe that this experimental phase of the ICBGs should be ended. The key is to learn from successes and failures so that future ICBGs and other similar development programs benefit from the combined experience of the ICBG program.

FIC should conduct analysis of the program to assure that the knowledge gained by the ICBGs to date is collected, analyzed, reported and disseminated. This is so important FIC should consider withholding a portion of funds available for grant activities should that be necessary. The analysis should address the kinds of scientific, economic, social and cultural, and political questions posed in this review. For example, it should compare the productivity of high through-put collection and screening against targeted screening based on leads from ethnopharmacological and ethnomedical knowledge; the relative contribution to conservation from a linkage to conservation; balance of screening for drugs for morbidity and mortality in local populations or in developed nations; and the potential for organisms other than plant

species to yield medicines and other beneficial uses.

The individual agreements for benefits sharing, for protection of rights to intellectual property, and for prior informed consent appear to be excellent and progressive adjuncts to the ICBG program. The analysis should review these tools and evaluate them for strengthes and weaknesses. A "tool kit" or guidelines for these kinds of agreements would be of great general interest beyond the ICBG program. A review of the agreements with an eye toward gaps or limitations that might be exploited when a local ICBG project policy or benefits sharing agreement is challenged, or when an important new drug is discovered, would also be of great use inside the ICGB program.

FIC staff are limited in the technical resources needed to conduct an analysis of the ICBG program and should not be expected to conduct the review. Rather they should look for a foundation with the broad interdisciplinary interests and expertise to analyze the ICBG program and provide advice and guidance to the FIC and the ICBG grantees. A foundation may find the project of sufficient interest to underwrite the costs. An evaluation contract would be the least attractive option. In any event, FIC staff (along with their funding partners) and ICBG grantees must be deeply involved in the analysis, from defining its scope through its report and recommendations.

III. Focus Questions

The FIC posed some "Focus Questions" in the materials sent to the reviewers. At the meeting, FIC staff, members of the Technical Advisory Group representing the federal institutes and agencies that co-fund the ICBGs, and scientists who received ICBG grants briefed the reviewers. The following responses to the Focus Questions have been constructed from the background materials, the briefings and individual, informal discussions between the reviewers and others participating in the meeting.

1. Does it appear that broadening of the original scope of the program is productive

in the context of the integrated goals of the program?

The reviewers believe that phytomedicines development generally offers one of the best initial targets for drug discovery screening. Local ethno-medical practices help focus the initial search. Screens of phytomedicines for other uses, including veterinary medicines and control of plant pests may also be productive. Additional possible uses as nutritional supplements, dyes, fragrances, and/or cosmetics may enhance the local acceptance of the ICBG program but these should not detract from the medical and public health goals of the program. These may also promote the program's conservation and economic incentive goals.

A focus on drug development to meet local needs and interests provides a base for drug development for diseases and conditions of broader interest. In addition it would serve as the foundation for a more ambitious program in drug discovery. Compounds derived from natural products should be sought for treatment of cancer and other chronic diseases as the local program matures in expertise and as procedures to identify high-priority candidates are implemented.

Expansion of discovery efforts to microorganisms or marine species should be considered as individual ICBGs mature and as opportunities arise. It may be more difficult to tie discovery to conservation in these areas. However a link between drug discovery from screening marine organisms in and around coral reefs presents an attractive opportunity to tie drug discovery with conservation.

2. Should future applicants be explicitly encouraged to consider small biotech companies and non-profit drug discovery groups as alternatives or additional partners? How significant are the likely tradeoffs in technical and financial resources for ICBGs?

ICBG grantees should be strongly encouraged but not mandated to solicit partnerships with small biotech companies. The same kind of encouragement should be given to inviting not-for-profit drug discovery groups to participate. The diseases of most concern in developing countries, namely TB, malaria and other parasitic diseases, etc. are most often not of interest to big pharma because the potential financial return is too low. Therefore, the ICBGs should work with academic groups

and government agencies that have expertise in these diseases. They should also explore the possibility that drug companies in the source countries might be interested in participating in the discovery, development and marketing of drugs for these diseases. There should also be thought given to how the decisions are made about whether a particular chemical entity has drug potential or not. If this is left only to big pharma partners, some promising compounds might get missed. In a big company, the criteria for moving a compound ahead are extremely demanding. For example, the compound of interest has to compete with other leads generated in-house by the company for the same disease indication. Often the second best compound is not advanced, but that doesn't necessarily mean it has no value. In addition, big companies often make a business decision about a compound independent of its ability to treat a disease. Thus a compound that might have promising drug potential may get dropped because the anticipated sales don't meet the requirements of a big company.

These are all legitimate reasons for the big pharma to not pursue a compound. However, some of these compounds might be of interest to smaller companies, companies in the source country where the business requirements are very different, or NIH. The natural product resources of the source countries are an important resource of chemical diversity and it is important to treat them as such to make sure that all the interesting compounds realize their true drug potential. As part of this, there has to be a clear recognition of the importance of getting effective patent protection on promising compounds before the structures are published in the open literature. Often publishing a structure before a patent has been filed destroys the compound's drug potential for companies. This creates an obvious tension for the ICBG grantees between the need/desire to publish versus drug discovery, particularly if the success of an ICBG and its ultimate renewal is partially measured by publications coming out of the project. The above is not meant to discount the potential role of big pharma, which has had and will continue to have a very important role to play in these programs. More than one partner, large or small, is likely to be needed.

3. *Are there some guidelines or trust-building activities that will facilitate maximum flow of data for research and a sense of confidence among participants and stakeholders regarding the destiny of data and samples?*

FIC cannot enforce a mandate for information sharing but should make every effort to encourage it. The RFA should include a plan for collaboration and information sharing with other ICBGs. FIC staff should strongly consider devoting one of two annual program meetings for technical collaboration in drug discovery (there is currently only a single joint annual meeting). The meeting would be closed and confidentiality agreements would be necessary.

FIC staff should put additional resources into their central data repository. It should be expanded to include program conservation data in addition to natural products. Grantees should be encouraged to participate in the design of the database and in determining rules for access to and uses of shared data.

4. *Is there evidence that either the involvement of indigenous communities and their traditional knowledge in drug discovery or in conservation/ development opportunities offer merit and should be given continued encouragement in the new application?*

Experience from the ICBG program and from research in ethno-pharmacology and ethno-medicine suggests that careful assessments of local medical practice provide productive leads for drug discovery- an observation that needs further evaluation. The ICBGs would benefit from substantially increased application of the expertise of sociologists with specialized training and experience in these fields to increase the constructive involvement of indigenous peoples. ICBGs should be urged to focus drug discovery initially on screening and development of phytomedicines and herbal products for treatment for diseases and conditions affecting local populations such as malaria and other parasitic diseases, HIV-AIDS, or other sexually transmitted diseases. Such focus should make the ICBG more meaningful and acceptable to the local population. Similarly, the local indigenous community must participate in identifying the options for use of the local biodiversity

and in setting priorities for its use. And compensation mechanisms must be created with the knowledge, understanding and consent of the local community.

5. *What lessons should be drawn from these events (the controversy surrounding the ICBG in Chiapas State in Mexico) and how might similar situations be avoided?*

This question indicates that FIC staff is taking the proper attitude in response to the position of groups that oppose globalization of trade and development and who directed this opposition to the ICBG grant in Mexico.

The controversy and events surrounding the project received wide publication in the science media and was the subject of a briefing session during the open session of the review meeting. The reviewers discussed the demise of the ICBG project in the State of Chiapas in Mexico in the closed session. No specific conclusions or recommendations regarding the circumstances were drawn, however some general guidance was offered. The loss of a project that was part of related activities in Chiapas that predated the ICBG grant and that was managed by scientists with outstanding reputations is troubling. It is likely that similar controversy will arise at another place in the world where an ICBG is operating. The program analysis recommended in the Consensus Observations above should investigate the circumstances in Chiapas to identify how such events can be avoided or better managed. The idea is to learn from the Chiapas incident, not to find fault with the program or its managers. Early signs of problems, strategies for coaching those involved, things to be avoided, and lessons learned are a few of the issues to be investigated. Clearly the situation in Mexico would benefit from careful analysis. There are many questions to be answered. How might problems have been prevented if given the benefit of hindsight? How should this experience shape the implementation of the third cycle of grants? What additional efforts might be made by FIC staff and by the US Department of State to assist the grantees and the ICBG program in advancing its goals? What are the arguments needed to either gain the support of the program opponents or that are effective in offsetting their opposition?

Who should make these arguments, to whom and in what settings?

6. Would progress toward the goal of economic development be substantially enhanced by including more formal economic research or expertise within the projects? Are there other types of activities compatible with the basic ICBG model that might enhance economic development?

The reviewers did not rule out a greater role for economic analysis, but assign a far greater priority to the need for business development expertise that would help ICBGs with preparing "business plans" for long-term viability of in-country development of natural products based on locally available natural sources.

7. As conservation is one of the principal goals of the program, what types of dissemination are most likely to produce conservation benefits today? How can this be encouraged?

In many cases, it was not clear from the presentations and background materials how the conservation efforts reported were linked to drug discovery at the local project level. Many appeared to be done to meet the requirement to include a conservation component in the grant. In some instances reports of successful conservation efforts appeared both unrelated and overstated. Conservation must be defined by local needs rather than by macro goals. Applicants for new ICBG grants and for competing renewals should demonstrate an understanding of local needs and the need to include local participants in the planning phase. Conservation does not necessarily mean protection from development. In fact, careful harvesting and cultivation may preserve species that are endangered. Use of plants and other natural product sources for drug development should not preclude the development of their use for other purposes.

8. What should be the appropriate balance of training in the ICBGs to ensure maximum contribution to health, conservation, and economic sustainability?

If resources are limited, training should only be at the graduate student, post-doctoral fellow, and visiting scientist level. Such individuals can return to the source countries and train additional students and technicians. Training technicians from

source countries does not have the same long-term propagation effect.

9. Have there been significant changes since 1997 in the science or the economic and political context in which these projects operate that would lessen enthusiasm for the ICBG approach? Are there significant concerns regarding the overall merit of renewing the ICBG program? What would be lost if this program were not to continue?

The reviewers are in complete support of the ICBG conceptual approach that integrates drug discovery, natural resource conservation and incentives for economic development. Their discussion at review meeting kept returning to the importance of continuing the ICBG program and concentrated on suggestions to both strengthen the approach and to maximize the potential for successful and sustained programs in developing countries. In fact, the reviewers all agreed that this question could have been the only question addressed during the review. In discussing the ICBG program, the reviewers considered not so much what would be lost if the ICBG program were not to continue but rather how great a potential the ICBG program has. Based on its performance to date it is clear that it continues to have a tremendous potential. Bioprospecting will continue whether the ICBG program does or does not. However termination of the program would leave a huge void in the leadership of how bioprospecting should be done in a responsible and equitable manner.

In addition to the Focus Questions, FIC staff sought advice from the reviewers on suggested levels of funding and technical support from FIC to the grantees and the proper role of FIC in the US and abroad in outreach, education, and program advocacy to policy makers, the general public, and the scientific community:

Level of Support- ICBG grants operate on about $500,000 to $750,000 per year from FIC and its co-funders. A portion of these funds are retained by the ICBG's parent institution to cover research overhead costs. FIC has taken every possible measure to assure that overhead costs are kept to a minimum. ICBGs have been unusually successful in obtaining funds from public and private sources and using FIC funds to leverage other grants. These funding arrangements reflect the innovation, successes,

and deep commitment of the ICBG principal investigators. The reviewers believe that about $750,000 per year is an adequate base. The aim is to provide adequate funding to assure that the ICBG project can operate, but not so much as to obviate the need to leverage funds from other sources.

Outreach and Advocacy- FIC should take a limited but active role in outreach, education, and public relations in support of the goals and methods of the ICBG program. There will surely be continued local and international debate about the ICBG program and similar activities, in particular fomented by groups and individuals who oppose economic globalization. FIC should implement efforts to reduce its impact on individual ICBG grant activities. ICBG project directors must be encouraged to pursue local efforts to create broad support for their projects at the local and national level. Local involvement in planning grants will be helpful as will outreach to the local media. As the ICBG's progress, the impact and benefits should be tracked and routinely reported locally and to FIC. Local or national workshops provide a good venue for such outreach and could be a part of the planning phase of new grants.

FIC staff can provide guidelines for local outreach and education but it is probably not necessary or appropriate that they be directly involved. FIC should continue to promote the ICBG's within the US. A major announcement of the next group of ICBG grants might set the stage for additional positive outreach. It is anticipated that the program analysis will produce findings that might be the subject of a meeting of grantees, the policy makers, industry, NGO's, foundations, and the science press. Such a meeting would advocate the ICBG program. As importantly, it should help assure that grantees fine tune their programs to follow the recommendations evolving from the analysis. Outreach education requires a fundamental understanding of the dynamics in the host country, thus it would be wise to involve an institution that specializes in outreach education to undertake or assist in such training.

IV. International Convention on Biological Diversity (CBD)

Lessons learned from the ICBG program will gain greater international acceptance and credibility if the US is viewed as supporting rather than opposing the principles contained in the CBD. Because the ICBG's operate in countries that have ratified the CBD, they must operate within its framework. It is the sense of the reviewers that current ICBG grantees may be limited in their efforts to establish local partnerships and programs linking drug discovery to conservation in the developing countries where they work. Local officials may mistakenly believe that as American scientists they must embrace the policies of the government of United States and that they oppose the CBD. The US is isolated by virtue of the fact that it has not ratified the CBD.

While the ICBG program is leading the effort worldwide to implement the principles of the CBD, the US does not receive enough credit for its leadership. The failure to ratify the CBD overshadows the contributions of the ICBG program. The ICBGs and the benefit sharing, development, and cooperation they promote are in the long-term interests of the US and would be promoted further if the US did ratify the CBD. The FIC should use its influence on policy makers in the National Institutes of Health, the Department of Health and Human Services, and the Department of State to encourage the US to ratify the Convention. The reviewers understand that such influence must be exercised with tact and confined to opportunities for internal discussion with the Department of State and US elected officials. The reviewers believe that the practical experiences gained from the ICBG program lends credibility to the FIC staff views on the CBD as it applies to drug development and conservation and could be persuasive in changing current US policy regarding the CBD.